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GENERAL

Relationship between Addiction to Narcotic Drugs and Crime

By H. J. Anslinger
United States Commissioner of Narcotics,
Representative of the United States to the Commission on Narcotic Drugs of the United Nations

Through the combined efforts of local, State, and Federal law enforcement officials, and the co-operation of the public, substantial progress has been made against the illicit traffic in narcotic drugs.

Before the passage of the first anti-opium law in 1909, addiction had become so widespread that imports of opium into the United States had reached the incredible amount of 628,177 pounds annually for 50 million population (this included 148,168 pounds of smoking opium, for which there is no medical use), whereas not more than 50,000 pounds would have been necessary then for medical purposes. In some of the country towns morphine and opium were sold by the grocers in large quantities. Addiction extended from the criminal underworld even to the so-called higher classes of the community and many were the crimes perpetrated by cocaine-crazed *habitués*.

Imports of narcotic drugs are now limited by the U.S. Bureau of Narcotics to strictly medical purposes, and average 350,000 pounds annually for 150 million people. Information indicates that the number of persons addicted to narcotic drugs has decreased by at least one-half since present policies went into force. The foregoing statement is not intended to convey the impression that we are not still confronted with a serious situation worthy of our best attention.

Some local law-enforcement officers will be able to contrast their experience with traffickers in narcotics many years ago, and their recollection of the traffic at that time, with the more favourable situation which exists today. During the First World War, one man in 1,500 was rejected because of drug addiction. During the Second World War, the Army Service Forces reported that roughly one man in 10,000 selective-service registrants examined for military duty was rejected primarily because of drug addiction.

However, due to post-war developments and conditions peculiar to certain localities, we are finding instances where there has recently been a retrogression and our hard-earned gains are being endangered.

There has been a disturbing revival in the heroin traffic to this country from the foreign ports which supply our illicit traffic, and violators must be more severely dealt with by the courts if we are to hold the line on addiction, and not lose ground.

* * *

The problem of narcotic drugs should be of vital interest to all law-enforcement officers. That *crime* and *narcotics* are interwoven is illustrated by the fact that violators of the narcotic laws head the list of all criminals in the United States having previous fingerprint records. This list includes persons convicted of offences ranging from vagrancy to robbery, forgery, counterfeiting, burglary, and other crimes. Of the narcotic-law violators arrested during a recent year, 63 per cent had previous records and arrests, whereas in the general arrests 42 per cent of the persons arrested had previous fingerprint records. In a study we made of a considerable group, taken at random from the records, it was learned that the first arrest for offences other than violation of the law on narcotics preceded, sometimes by as much as eight to ten years, the time when addiction to narcotic drugs began. This confirmed a study conducted by the United States Public Health Service wherein the fact was forcibly brought out that a criminal addict was, in the vast majority of cases, a criminal before he became addicted; in fact, in 225 cases studied at that

time, every criminal among them had committed some crime before the use of narcotics was begun.

From our studies, it can definitely be concluded that drug addiction is one of the later phases of the career of the criminal addict (but this study applied only to addiction to opium and its derivatives, and not to marihuana, the use of which is frequently a prelude to crime).

On 30 June 1949, out of a total prison population of 18,531 convicted of Federal offences, 1,759 were serving sentences imposed under the Federal laws relating to narcotic drugs and marihuana. With 2 per cent of the Federal personnel concerned with enforcing criminal laws, the Bureau of Narcotics accounts for approximately 10 per cent of the commitments to Federal prisons.

For every agent in the field service of the Narcotics Bureau, there are confined in the Federal penitentiaries and other institutions ten convicted violators of the laws on narcotics. Many of these convicts have some of the worst criminal records in the United States for major crimes.

It is well established that a large proportion of the pickpocket artists, the shoplifters, the professional gamblers and card sharks, the confidence men operating fake horse race or fake stock sale schemes, the "short con" men such as the "short change artists" or the coin matchers, are addicted to the use of narcotic drugs. By the very nature of their criminal activities, they are required to be migratory and could be classed as roving criminals. No community seems to be entirely free of their depradations and activities. Particularly is this true of tourist centres and other places where large crowds congregate.

A skilled gang of pickpockets can steal and will steal an average of sixty pocketbooks a day, and a good day's work will net them $1,500 or more. The "elite" of the confidence men, preying on the gullible, may have incomes that reach really impressive figures.

The records of criminals, of the type referred to, usually disclose numerous arrests; but it is interesting to note that in the majority of cases the charges were merely vagrancy or suspicion. This no doubt was due to the very nature of their criminal activities, which makes it difficult to apprehend them in the commission of the crimes in which they specialize, and still more difficult to obtain sufficient evidence to secure a successful prosecution. The criminal is released from custody by the posting of a small cash bond and as a rule fails to appear to answer the charges.

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In view of the high percentage of addiction among these criminals, it is suggested that a thorough and systematic search for narcotic drugs be made of their persons, effects, baggage, rooms, and automobiles. The search should be conducted by at least two officers, not only for completeness but to assure corroboration in case of prosecution. It should be thoroughly systematic from the head to the feet. The suspect should be disrobed and his wearing apparel minutely examined. (The disrobing is important because narcotic drugs have frequently been found attached to intimate and other parts of the prisoners' anatomy.) They also have been found concealed in hat-bands, neckties, seams of clothing, hidden small pockets in coats, vests, trousers, and also in the cuffs of the trousers, in fountain pens and watches, as well as in the heels and inner soles of shoes. These suggestions apply to female as well as to male suspects.

Instances have occurred where pockets of trousers, handkerchiefs, and sheets of paper have been saturated with a concentrated solution of a narcotic, thus assuring a supply in case of arrest and detention. These devices are known in the vernacular as sachets.

The search of rooms and living quarters presents a more difficult problem due to the ease with which narcotic drugs can be concealed. Here a thorough and systematic search should be conducted, starting with some focal point. Narcotics have been found hidden in the bottoms of talcum-powder cans and other cosmetic containers, fixtures, bedsteads, window-sills, chandeliers, door knobs, rear of dresser drawers, secret plants in the woodwork, and many other places too numerous to mention.

Baggage and trunks should be searched for secret compartments.

Narcotics have been found concealed in hub-caps, rear of headlights, spare tyres and tubes, and many other secret places in automobiles. Under certain circumstances, vehicles used for the transportation and concealment of narcotic drugs can be seized and forfeited to the United States Government.

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Often local officers can be of considerable assistance if, when arresting dealers in narcotics, they will look particularly for indications of the source of supply of the drugs. Most drugs in the illicit traffic must be smuggled into the country originally and, therefore, it follows that dealers and users of drugs inland must be supplied from coastal or border points. Sometimes deliveries are made by dealers in person but often drugs may be shipped by mail, express, or baggage. Often upon the persons or premises of an arrested dealer will be found communications, usually written in a guarded manner, as well as telephone numbers and addresses. Since whole-

sale dealers in illicit narcotics, in distributing centres, often play a comparatively safe game by shipping their wares to distant points only, without catering to any local trade, information of the sort indicated, if conveyed to the proper authorities may prove to be particularly helpful in locating, and eventually apprehending distant wholesalers. In this connexion, it should be borne in mind that ordinary trade or geographical considerations do not always govern the distribution of illicit narcotic drugs. Someone on the Pacific Coast, close to a seaport where, ordinarily, it would be thought that narcotics would be available, may nevertheless send to New York for his illicit drugs because of price or personal considerations. Relevant documentary evidence, as well as all narcotic drugs found, should be duly identified by all the seizing or searching officers, in order to ensure its acceptance as evidence in court.

In carrying out enforcement activities against those who are both criminals and addicts, the utmost caution should be exercised, and the officer should never relax his guard for a moment, otherwise tragedy may ensue from the viciousness and recklessness of this type of criminal.

On Sunday morning, 24 September 1950, our Narcotic District Supervisor Anker M. Bangs was shot to death by a narcotic addict while search was being made of the addict's living quarters. This is merely one example from hundreds of cases in which law-enforcement officers have been killed or grievously wounded by drug addicts.

Imitation Morphine Tablets in the Illicit Traffic

A series of examples of the ingenuity of the illicit trafficker in breaking the law.

The nature, supply, and distribution of drugs used for narcotic addiction have undergone many changes. One of the most evil was the change from the crude drugs, of which the worst was opium, to the purified, active principles and derivatives, such as morphine, heroin, and cocaine. Beneficent in medicine when used for the relief of pain and surcease from suffering, these same drugs, in their use by addicts, have brought misery, degradation, and crime, beyond telling.

A landmark in the struggle against narcotic addiction was the adoption of the "Convention for Limiting the Manufacture and Regulating the Distribution of Narcotic Drugs", also known as the 1931 Convention. Prior to that time, huge quantities of narcotic drugs, manufactured ostensibly for medical purposes, were escaping from control and were being used for the purpose of addiction.

The 1931 Convention has been very successful, but illicit dealers in narcotics have not ceased their activities. For a time, some factories shifted from country to country, setting themselves up where the laws were most lax and trying to maintain a semblance of legality while still pouring out a flood of narcotics into illicit channels. As successive countries adopted more stringent controls, these activities became more and more concealed. Broadly speaking, the manufacture of narcotic drugs in known factories is now limited to the legitimate medical and scientific needs of the world. There is some diversion to illicit purposes, of course, but this is no longer the main source of the narcotic "white drugs" of addiction, and is of minor importance compared to their manufacture in concealed, illicit laboratories.

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The drying up of many sources of supply and the tightening of controls all the way along the line, resulted in enormous increases in the price paid by addicts for drugs. Still the demand exceeds the supply, so that adulteration and dilution of the drug is quite general. In the United States, the principal drug of addiction is heroin but the pure salt of heroin is almost unknown in the illicit traffic. The most common adulterants are quinine, which is present more often than not, and procaine; in addition virtually every dealer who handles the drug illicitly takes his turn in diluting it with lactose (milk sugar), sucrose (ordinary powdered sugar), mannitol, or some other inert substance.

Many addicts in the United States think that heroin is a weaker narcotic than morphine, though in reality it is much stronger. The manufacture of heroin has been prohibited in this country for many years, and the addicts know only the illegal, adulterated, diluted drug. On the other hand, they can sometimes get legal morphine on prescription—this often involving forgery or some other crime, at which the confirmed addict does not hesitate. Also morphine can sometimes be stolen from a drugstore. The addict's acquaintance with legal morphine leads him to believe that it is the stronger drug.

In such circumstances, diverted or stolen drugs in their original packages command especially high prices in the illicit traffic. The racketeers and other criminals who prey on the addicts while supplying them with narcotics know this, of course. They do not actually have stolen narcotics for sale very often, but much more often they counterfeit labels, containers, and revenue stamps, in order to enhance the price of the narcotics.

An interesting case of this kind occurred in the United States, during 1948-1950. In fact, any number of cases of law-breaking were involved, as the counterfeit "morphine pills" were spread over almost the entire

country. Indeed the first discovery was made in the Philippines. The "Philippine angle" was never entirely cleared up as to its connexion, if any, with later developments.

In May 1948, a seizure was made in the Philippines of 1,222 vials labelled:

"20 soluble Hypodermic Tablets No. 3,
"Morphine Sulfate U.S.P.
"¼ grain (0.0016 grm). Poison.
"Warning—May be habit forming. Caution. To be used only by or on the prescription of a physician.
"Property of the United States 1334139.
"John Wyeth & Brother, Inc. Philadelphia, Pa."

The label was a good imitation. The tax stamp was counterfeit. No narcotic at all was found in the tablets; in this case the tablets were simply a fraud on any purchaser.

In September 1948, a passenger from Manila was picked up as he arrived at the airport of Honolulu, Hawaii, and found in possession of a large supply of counterfeit labels.

In the early part of December 1948 narcotics investigators in Kansas City, Missouri, found that tubes containing what purported to be morphine hypodermic tablets were being sold in Kansas City. Two peddlers there were buying them, about $700 worth at a time, at $20 per tube of 20 tablets labelled as ¼ grain tablets of morphine sulphate or $4 per grain. Legitimately such tablets—if they had been genuine—would have been worth about 70 cents per tube, or 14 cents per grain. They were being sold to other addicts by the two peddlers at $7 per grain.

These tablets were found to contain poorly acetylated heroin as the narcotic.

At about the same time, a similar tube and tablets were found in South Carolina, in the possession of a doctor who had been supplying addicts. He admitted having obtained it from a man and wife running a gasoline service station in North Carolina, a pair believed to have dealt in counterfeit ration coupons for gasoline, during the war. This tube had the label—counterfeit of course—of Merck & Co.

The Kansas City tubes bore the Wyeth label, like those seized in the Philippines. But some peculiarities were noted. The narcotic stamp was overprinted with "E R S & S", presumably standing for E. R. Squibb & Sons. Doubtless this had been copied from a genuine stamp on a Squibb tube, then used with the counterfeit Wyeth label. One tube was found on which "hypodermic" was spelled "hyopdermic". Also on some tubes the cancellation date of the narcotic tax stamp appeared to be 8 December 1949, although the tubes were obtained in December 1948.

In 1949, the tubes and tablets began to be found in many parts of the United States. Seizures were made especially in New York City, Chicago, Philadelphia, and in the Carolinas. Some tubes bore an E. R. Squibb label and some a Parke-Davis label, counterfeit of course. Another Wyeth label was also found, which had "Philadelphia" abbreviated as "Philada". On the same label the decimal comma was used for the gramme equivalent, instead of the decimal point which is customary in the United States.

Although there were so many different labels it seemed likely that the tubes were coming, probably not exactly from a single source, but from some kind of loose association of racketeers, counterfeiters, and dealers in illicit narcotics. Strenuous efforts were made to trace the glass tubes or vials, but without any definite result. There was only one glass manufacturer in this country making a similar tube at the time, but an exact match for the tubes illegally used could not be found in the legal trade.

The tablets themselves were counterfeit. They varied considerably in composition but there was a general similarity. Nearly all of them purported to contain ¼ grain morphine sulphate but instead contained heroin hydrochloride which, when hydrolyzed to morphine, amounted to about 1/12 to 1/24 grain. Since heroin is considerably stronger than morphine the users may not have felt too badly cheated. All the tablets also contained another alkaloid, brucine. This was unquestionably put in to imitate the morphine reaction with nitric acid, in case anyone got suspicious and applied this generally known test, in which morphine differs from heroin. The "heroin" was sometimes straight diacetylmorphine and in other cases was rather poorly acetylated (or possibly, had been partly hydrolyzed in making the pills), so that the pills contained some morphine and monoacetyl-morphine as well as diacetylmorphine. All contained corn starch and lactose also. In the earlier analyses benzoic acid was generally found; later, benzocaine was found instead of benzoic acid. In a few cases quinine was present. Some of the pills became more or less brown with age while others remained white.

It is possible that some of the adulterants were already present in the "heroin" used, and were not intentionally added in making the pills. In one New York case both bulk "heroin" and "morphine" tablets were seized. This "heroin" contained heroin (diacetylmorphine) hydrochloride, benzoic acid, quinine, and small amounts of lactose and starch. The "morphine" tablets contained heroin hydrochloride, brucine, quinine, lactose, and starch, and some of the tablets also contained morphine hydrochloride.

The tablets had a considerable distribution in the Carolinas. There are certain regions in these states where morphine addiction is almost endemic, dating back to the time before there were any laws controlling nar-

cotics, and it has been impossible so far to stamp it out completely.

A case was made against a dealer, X. Y., who was also an addict himself. When arrested, he told the narcotic agents the full story of his recent activities in dealing in narcotics.

He began his account with 1947. In the early part of this year, and previously, he had dealt in "Spanish type" morphine labelled "Medical Depot, Madras" and "English type" morphine labelled "Burroughs and Wellcome". 100 grains of the "English" morphine cost $275. An ex-convict, W. Z., who had served about three years in prison on a black-market charge, was employed by X. Y. in running liquor from Baltimore into "dry" territory, and later in his narcotic transactions. About the middle of the year X. Y. was offered 200 bottles of "good stolen morphine" with 60 grains to the bottle at $2.50 a grain. He took four bottles, paying $600. In September 1947 he was offered the tubes of "morphine", which in this case had the Merck label and were claimed to have been stolen by a night watchman from Merck and Co. X. Y. bought 1,500 grains (according to the label) in tubes and paid $2,250 for the 300 tubes. He got suspicious of the genuineness because all the tubes had the same number. On 2 October 1947 he bought ¼ kilo of heroin for $2,550 and 500 grains of the tube morphine—"Merck"—at $1.50 a grain. On 1 November 1947 he bought 1,200 grains of the "phony morphine" as he was now calling it, at $1.40 a grain, a total of $1,680. With continued dealing, X. Y. got the price at which he bought down to $1.15 and finally down to 90 cents a grain (the value of real morphine tablets sold legally being only about 14 cents per grain). He got the price of heroin down to as "low" as $1,200 per ¼ kilo. He sold the phony morphine at up to $2.50 per grain. His principal customers were themselves dealers and peddlers; some were users of the drugs themselves and some were not. They paid around $300 to $500 at a time, or even more.

A few of the other transactions of X. Y. may be mentioned. June 1948, ¼ kilo of heroin bought for $1,800; 15 September 1949, ¼ kilo of heroin for $1,400; 22 October 1949, $1,200 paid for ¼ kilo of heroin and $900 for 1,000 grains of the phony morphine; 28 November 1949, 4 ounces of heroin and 1,000 grains of phony morphine for $1,700.

As a result of intensive work by the narcotic agents, and partly from information supplied by X. Y., a number of dealers in illicit narcotics in the Carolinas were arrested, tried, and convicted. Some sentences were: Henry Gainey, ten years; Paul Sadler, seven years; Willie Dudley, three years; Howard Overman, four years; Ned Welch, three and a half years; Nathan Cheek, five years; John Muse, eighteen months plus a two-year sentence suspended for five years probation; M. G. Batson, two years; Fred Green, three years. One narcotic dealer was also a bootlegger and on conviction of bootlegging was sentenced to two years in prison and a $35,000 fine.

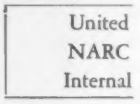
At Chicago, Michael Filishio and Frank Tovar were each sentenced to five years for a heroin case and counterfeiting.

The pills only began appearing on the Pacific Coast—to the knowledge of the narcotic agents, at least—in 1950. On 17 February 1950 there was a seizure in California of six bottles each containing 100 of the ¼ grain "morphine" tablets. In general, however, during 1950 these pills began to disappear from the traffic in illicit narcotics.

Most of the illicit narcotics of the United States are distributed from New York City, and these pills were no exception. One important source, Peter Locascio, was arrested in New York in possession of 5½ pounds of heroin and 3,048 vials of "morphine", each containing 20 tablets and bearing counterfeit labels and stamps.

An attempt to order a plate from an engraver revealed a method of obtaining plates for the counterfeit tax stamps. The plate asked for was to read:

Evidently it was to be cut in two, the right half to be joined to another half-plate which would have on it,



In fact some of the counterfeit stamps on morphine tubes showed printing from two plates joined together.

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It is not possible to give anything approaching a full account of the cases arising out of the investigations of these morphine tablets. In fact many are still pending in the courts and it will be years before the story can be completed.

The special dangers of such pills in the illicit traffic are obvious. For example, a criminal pharmacist could stock them for sale to addicts, and still not appear to have anything but legal narcotic supplies if his store were given a superficial inspection or even raided by the police. In general in the United States this was not done; the sale of the pills was usually through completely illegal channels, and the labels were rather a fraud on the miserable addicts than an attempt to disguise the traffic with any semblance of legality. The backbone of this particular traffic in the United States has been broken. Narcotic authorities in other countries should be alert to see that it does not establish itself anywhere else.

TECHNICAL

Present State of the Chemistry of Opium and its Future Possibilities

The composition of opium is not yet wholly known. From a scientific as well as a commercial point of view, it is necessary to explore further the rare alkaloids it contains and to devise methods of assaying them.

It is generally believed that opium has been very thoroughly examined, so that all its alkaloids are well-known, with the possible exception of one or two present in only infinitesimal quantities.

This is not the case. The chief investigations of opium for minor alkaloids were made over 75 years ago, by Hesse. For the time, the work was magnificent, but it was not actually complete. Moreover, the statements now in the books about the characteristics of at least some eight or ten of the alkaloids that were discovered, are so meagre and even inaccurate that it is quite impossible to recognize these alkaloids as they are analytically isolated, without exhaustive investigations—even knowing that they come from opium, and even though they are actually present in amounts many times as great as the minute percentages attributed to them.

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For example, a minor phenolic alkaloid, which accompanies morphine in most extractions, can be isolated from less than half a gram of opium, so as to be easily recognized by colour reactions. In fact, it probably constitutes at least 0.1 per cent, possibly 0.2 per cent, of many opiums. It is titratable and its presence thus introduces an error of about 1 to 2 per cent into many morphine assays by extractive methods (irrespective of other possible errors). It may be codamine. Codamine is said to give a "dark green" colour with nitric acid, gradually becoming lighter; the deep green colour with nitric acid is supposed to distinguish it from any of the other opium alkaloids. With the extracted alkaloid, nitric acid does indeed strike green, but this colour instantly vanishes, and a strong yellow-brown promptly develops. The reaction found is of the glaucine type. In fact, this alkaloid, which far exceeds the percentage attributed to codamine (only 0.0033 per cent), in colour reactions much more closely resembles glaucidine—a minor phenolic alkaloid isolated from *Papaver orientale* by Gadamer and Klee—than it does the codamine described by Hesse.

Moreover, there is another minor phenolic alkaloid in opium that also gives the nitric acid reaction and other glaucidine-type reactions. Perhaps it, instead of the alkaloid that so closely accompanies morphine, is codamine, though the description of the properties of codamine fits even less well in this case. At any rate it seems that at least one of these alkaloids has never been "officially" discovered.

One minor alkaloid of opium is easily characterized by its property of yielding an intense purplish-red colour when its solution in dilute mineral acid is tested. In the lists of opium alkaloids in books, it appears three times under different names: rhoeadine, porphyroxine, and meconidine. The true rhoeadine, alkaloid of *Papaver rhoeas,* does not exist in opium. The properties ascribed to "porphyroxine" are all wrong; the last "porphyroxine" (Rakshit's) was probably impure codeine. Hesse's "meconidine" was never obtained in crystalline form and actually must have been a mixture of phenolic alkaloids. The real red-turning alkaloid has been isolated in crystalline form by the writer, but only on a rather small scale by extractive methods, and no determination of the elementary or constitutional formula has yet been made. (See E/CN.7/117, 14 April 1948, part II D, Some Minor Alkaloids of Opium, Alkaloid I, "Porphyroxine-Meconidine".)

In working up about 2 pounds of opium (primarily for "porphyroxine-meconidine") a minor phenolic alkaloid was obtained which was probably laudanine. However, it was extractable by chloroform from alkali solution, contrary to the statements about laudanine.

Of seven minor phenolic alkaloids either isolated or otherwise noted in this investigation, not a single one

except the "porphyroxine-meconidine" (which was wrongly described) could be recognized, with any complete assurance, as being a previously-named alkaloid of opium.

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To remedy this situation intensive investigation is needed. A thorough investigation on no more than 10 kilograms of opium would most probably show what alkaloids, of those that can be recognized in even a few grams of opium by solvent-extraction methods and colour tests, are to be regarded as having been already discovered and named, even if not correctly described in all respects. A more extensive investigation ought to be made, for the reason that at the same time several new phenolic alkaloids could almost certainly be discovered.

Particular attention ought to be given also to water-soluble bases that are extracted but very slightly, if at all, by ether and other immiscible solvents. The neglect in this field may be illustrated by a related case that has now been clarified, but only recently. Selmi, in 1876, wrote of the discovery of an "alkaloid" in the green capsules of *Papaver rhoeas* which, in its solubility in amyl alcohol but not in most immiscible solvents, and in certain reactions, including the yielding of crystals with iodine-HI solution, showed certain similarities to morphine with respect to properties and reactions used in toxicological identifications. He specifically said that it was not morphine. Hesse, previously the discoverer of rhoeadine (alkaloid of *Papaver rhoeas*), thereupon re-examined *Papaver rhoeas,* but in such a way as to fail completely even to discover what Selmi was talking about—which seems to have been, so far as a nitrogenous base is concerned, a very conspicuous content of choline. This episode appears in a number of books of reference which refer to Selmi as having claimed to find morphine in *Papaver rhoeas,* and the claim refuted by Hesse. (See *The Opium Poppy and Other Poppies,* issued by the U.S. Treasury Department, Bureau of Narcotics, Washington, 1944; pages 57-58, 77-78.)

Returning to opium, there is ample evidence of the presence of nitrogenous bases not included within the scope of the original searches for alkaloids. Because of the poor solubility of morphine in any very useful immiscible solvent, extractive separations of morphine are generally made with a combination of solvents such as chloroform-ethanol, chloroform-isopropanol, or benzene-isopropanol. By reason of some solubility in ethanol or isopropanol, these water-soluble compounds of basic nitrogen usually contaminate the morphine extract. They do not seem to be titrated with the morphine and may be either very feeble bases or, perhaps, strong bases the salts of which are partially extracted, while the bases themselves are either volatile or not even set free by ammonia.

In examining young seedlings of the opium poppy, the writer found one such compound rather conspicuously present. Crystals with a gold bromide reagent could be obtained to characterize it, but it was never identified nor even further studied. Could it be the precursor of morphine?—for very probably the plant constructs morphine out of some simpler compound.

Here we may note that Annett, Sen, and Singh reported that, while the opium from successive scarifications shows a rapid and large fall in morphine content, the percentage of nitrogen remains practically constant. ("Investigations on Indian Opium, No. 1", Memoirs of the Department of Agriculture in India, vol. 6, No. 1, pages 1 to 154.) The substance or substances making up the difference are unknown.

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New and really thorough investigations of opium for its alkaloids and other nitrogenous bases are highly desirable from all points of view: scientific, practical, commercial, analytical, chemical, botanical. The pure scientist will doubtless be rewarded more than others, but the need is evident from purely analytical researches. Since former scientific researches were chiefly on Turkish opium, it is probable that new alkaloids can most easily be discovered, or found in greater quantity, in some other kind, such as Iranian or Indian. Minimum requirements for the amount of opium are not so excessive as might be supposed: considering the development of microchemistry, it is possible that 10 kilograms now will go nearly as far in experienced hands as a ton in Hesse's day. The Canadian chemist of the Organic Chemistry and Narcotic Section, Food and Drug Divisions, Department of National Health and Welfare, who is already collaborating in the United Nations inquiry on the methods of determining the origin of seized opium by chemical and physical means, has indicated that he intends to make such fundamental investigations as he can, particularly for the minor phenolic alkaloids, old and new. There seems to be room for other investigations which would overlap his only slightly or not at all.

Nothing has been said in the foregoing about the non-nitrogenous constituents of opium. Some of the known non-nitrogenous compounds, for example meconic acid and meconin, are of considerable interest, and practically are known only from opium and the opium poppy plant. The water-soluble constituents of poppy chaff, after extraction of the alkaloids, have been studied by Karrer and Schmid (Helvetica Chimica Acta, 1945, *28,* 722); these constituents may or may not be about the same in opium.

Little is known about the opium fat or wax, the odorous substances present, the coloured compounds—not present in the opium (poppy juice) as it comes from the plant, etc. It is very probable that investigation of the non-nitrogenous compounds of opium would also be interesting, valuable, and scientifically rewarding.

Statistical Studies on the Mortality Rates and the Causes of Death among the Opium Addicts in Formosa

By Professor Tsungming Tu

The author, a member of the Pharmacological Institute of the National Taiwan University, Taipeh (Formosa), has been collecting data since 1928 on the opium used in Formosa. He sets forth in the present article, with detailed statistics from the years 1923 to 1933, the repercussion of opium addiction on morbidity and mortality rates and concludes that the mortality rate is much higher for the inveterate opium addicts.

There is no exact statistical study available about the influence of habitual opium or morphine use upon any race or other subdivision of mankind as a whole. For an investigation of this problem, the conditions, as they exist in Formosa, are especially favourable, perhaps more favourable than anywhere else in the whole world, because on the one hand stringent official control has been exercised over the habitual users and the suppliers of opium, and on the other hand a complete census of the population has been effected and is always brought up to date at regular intervals. Thus the question is important not only from the toxicological point of view, but also from that of social sanitation.

Since 1928 the author has been collecting data as they became available, and has already published many reports dealing with various aspects of the problem of the consumption of opium in Formosa, and especially the following: the changes in the number of opium addicts during the last 38 years and in the quantity of prepared opium consumed during that time; the age at which opium smoking was started; the motives leading to opium smoking; the degrees of addiction; certain physical peculiarities of the addicts; the rates of childbirth by female addicts, and by nonaddicted wives of male addicts; the annual death rate; the occupation, education, criminality, etc. of the addicts.

* * *

Today's communication has, as its main object, the mortality of all the Formosan licensed opium addicts during the ten years between the end of 1923 and the end of 1933, examining it under various conditions and establishing comparisons among the various components.

The results obtained so far may be given in outline as follows:

(1) In 1897 the Government of Formosa took on a policy of gradual abolition of opium smoking and opium eating, and since then the number of opium addicts has greatly decreased. Taking their number in September 1900 as the starting point, we find the following reductions: September 1900, number of addicts 169,064, percentage to the whole population, 6.3, index 100; end of 1929, number of addicts, 24,626, percentage of the whole population, 0.6, index 15; end of 1937, number of addicts, 11,960, percentage to the whole population, 0.23, index 7. The quantity of prepared opium sold by the Formosan Monopoly Bureau decreased from 200,927 kilograms in 1900 to only 16,020 kilograms in 1937, but the average dose allowed to individual addicts remained between 3 and 4 grams per day. In 1941, we began the treatment of the licensed opium addicts,

removing their addiction completely, and in 1946 this work was completed and the Government Central Hospital for Opium Addicts in Taihoku was closed.

(2) The average yearly death rate of the licensed opium addicts in the whole island for the 35 years from 1901 to 1935 was 65.5 per 1,000 of the addict population, while that of the general population amounted to 26.1. If the annual changes of the two rates are compared, the figures for the general population show a tendency to diminish, whereas those for the addicts are constantly increasing.

(3) In order to compare the mortality rates as depending on age and sex, the licensed addicts living during the 10 years from the end of 1923 were classified according to their number of years, starting with 15 and reaching the highest figure with 90 years. For this purpose the arithmetic mean of x years of life at the beginning and the end of each calendar year was used considering this as the nearest practically attainable approximation to the actual age of the addicts.

At the end of 1923 the number of licensed addicts in Formosa was 40,981, comprising 35,189 males and 5,792 females. During the ensuing 10 years the number of deaths registered among the licensed addicts amounted to 19,212, of which 16,497 were males, 2,715 females.

(4) From this data it may be seen that the total mortality rate per 10,000 of the population was 596.1 for the 19,212 licensed opium addicts, deceased during the 10 years and 197.7 for the general population over 20 years of age during the same period. Among the 18 groups the highest rate, i.e., 165.6 for the addicts against 51.8 for the general population, was occupied by diseases of the respiratory system. Also in the six groups infectious and parasitic diseases, diseases of the digestive system, diseases of the genito-urinary system, senility, diseases of the circulatory system, diseases of the nervous system and the special sense organs, the rates for the addicts were much higher than those for the general population. Only slightly higher rates for the addicts than for the general population appear in the following four groups: Cancer and other tumours, death from external causes, rheumatic diseases, etc., alcoholism, etc. In the group, diseases of the skin and the subcutaneous tissue, the rate for the addicts is equal to that for the general population. In the group pregnancy, etc., the number of deaths among the addicts was only two, with a mortality rate of 0.4, against 66 for the general female population.

(5) We also compared the death rates of the opium addicts with those of the general population, both divided according to decades of age and according to 18 groups of diseases. During the first two decades, from 20 to 29 years and from 30 to 39 years of age, no clear-marked differences can be established between the addicts and the general population, because the number of addicts deceased at 40 or below is too small. In the higher decades, however, certain disparities become gradually manifest. Thus in the decade from 40 to 49 years there have been no deaths from senility among the general population, while for the addicts we find a mortality rate of 1.64 per 10,000. In the group diseases of pregnancy, etc., the mortality of the female addicts amounts to 2.07 against 4.22 for the general female population. In the age group from 50 to 59 years the mortality from senility rises to 10.55 for the addicts against only 0.75 for the general population; in the same age group there were no deaths from diseases of pregnancy, etc., among the addicts, but 23 deaths, with a mortality rate of 0.17, among the general female population.

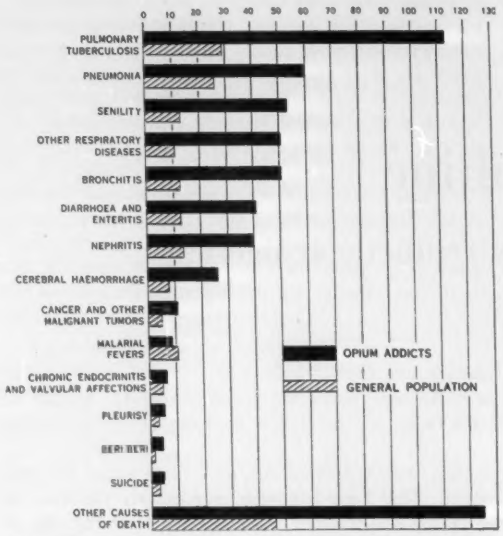
(6) If the mortality rates are given separately for quinquennial age groups among the addicts and the general population, and the influence of the disease of the respiratory system upon those rates is ascertained, we find in general that the trends are identical both for the addicts and the general population, but the rate is clearly much higher in the case of the addicts, the only exception being the age group between 30 and 34 in which the number of addicts and of deaths is low. In the higher age groups the rates are: for the ages between 35 and 39 years, 40.90 per 10,000 addicts against 38.43 per 10,000 of the general population, for the ages from 40 to 44 years, 62.17 against 48.79, for the ages from 45 to 49 years, 86.84 against 55.59, for the ages from 50 to 54 years, 129.14, against 71.93, for the ages from 55 to 59 years, 166.07 against 88.25, and for the ages of 60 and more years, 252.64 against 183.7.

(7) If instead of diseases of the respiratory system only pneumonia is considered, the results do not greatly differ. At the ages from 30 to 34, the figures are too low both in regard to the number of addicts and the number of deaths among them. For the ages from 35 to 39 years and from 40 to 44 years there is no difference between the addicts and the general population. But in all the 5-year groups above 44 years, the addicts show decidedly higher rates than the general population, the range varying between 8 and 27 per 10,000 of the two populations.

(8) If the principal causes of death among the addicts are compared with those among the general population of more than 20 years, the following details may be extracted from diagram no. 1: Among the addicts the most frequent cause of death is pulmonary tuberculosis, with 3,611 deaths during the 10 years, and a mortality rate of 112.04 per 10,000 population; next comes pneumonia, with 1,923 deaths, and a mortality rate of 59.67; the third place is occupied by senility, with 1,708 deaths, and a mortality rate of 53.00. These three diseases are followed by other diseases of the res-

Diagram No. 1

Mortality Rates from Principal Causes of Death of Licensed Opium Addicts and of the General Population over 20 years of age



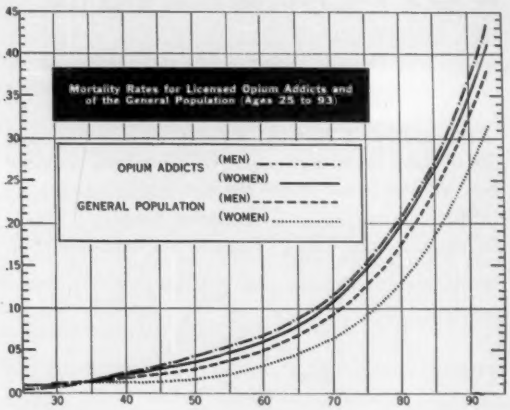
piratory system (chiefly asthma, but not comprising tuberculosis, bronchitis, pneumonia, pleurisy), bronchitis, diarrhoea plus enteritis, nephritis, cerebral hemorrhage, cancer plus other malignant tumours, decreasing in that order, with mortality rates ranging from 50.30 at the highest to 10.80 at the lowest. Still lower places are occupied by malarial fevers, heart diseases, pleurisy, beri-beri, suicide, with mortality rates decreasing from 8.56 down to 4.44.

Among the general population over 20 years the most important cause of death is likewise pulmonary tuberculosis, however with a mortality rate of only 28.98 per 10,000; next comes likewise pneumonia with a death rate of 25.96; the third place is occupied by nephritis, with a mortality rate of 13.13. These three diseases are followed by diarrhoea plus enteritis, senility, bronchitis, other diseases of the respiratory system (chiefly asthma, but not comprising tuberculosis, pneumonia, pleurisy), malarial fever, decreasing in that order, with mortality rates ranging from 12.93 to 10.39. The lowest places are occupied by cerebral hemorrhage, heart diseases, cancer plus other malignant tumours, suicide, pleurisy, beri-beri, with mortality rates decreasing from 7.72 down to 1.42.

The total mortality rate from all causes not specially named in the preceding amounts to 124.45 for the addicts, and to 46.73 for the general population.

(9) From the above statistics it appears that the evil consequences of the habitual use of opium in relation to the expectation of life do not show at once, inasmuch as during the early years, viz., from 25 to 35, there is no marked difference between the mortality rate of the addicts and that of the general population. But beginning approximately with the ages from 35 to 40, the adverse influence becomes gradually manifest, and above 44 years the rate of mortality is always higher among the addicts. Especially is it worth noticing that between 45 and 92-3 years of age, when the rate of mortality reaches its peak, the mortality rate among addicts increases usually by from 15 to 35, in the most extreme case by 50.77 above the value per 1,000 of the general population considering only the male addicts; but if the female addict population alone is considered, the figures rise by between 20 and 70, in the most extreme case by 92.64 (see diagram no. 2).

Diagram No. 2



* * *

In conclusion to this report may I be permitted to place special stress upon a few points that, in my opinion, deserve the utmost attention, namely: by far the greatest part of opium smokers start smoking opium in their twenties and early thirties, and then acquire the habit within a few years later, that is, in that part of their lives which is the most valuable not only for each individual, but also for the whole community, if we consider the question from a sociological standpoint. During these earliest years, and for a few years afterwards, the rate of mortality does not seem to be greatly affected; but we need only look at those cases in which the habit has persisted for 10 years or more, and it will become manifest that opium smoking is bound to exercise an injurious, and finally a ruinous influence upon the constitution of the body, raising the mortality rate high above that of the general population.

The Structure of Morphine

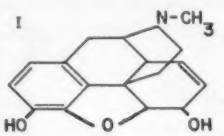
Chemistry of the totally or partially synthetic analgesics

By Paul B. Weill, Ph.D., and Ulrich Weiss, D.Sc.

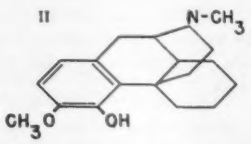
INTRODUCTION

The history of chemical research on morphine and the alkaloids chemically related to it has been described in a previous article in this *Bulletin*.*

The main arguments in favour of formula I, below, for morphine proposed by Gulland and Robinson[1]** in



1925 were set out in that article, together with the objections to its unanimous adoption. The article ended with the hope that the synthetic experiments now in progress would provide the irrefutable proof so long awaited. That hope has been very quickly fulfilled. In the remarkable research work referred to at the end of the previous article, Grewe *et al*[2] have confirmed Gulland and Robinson's formula by a total synthesis of tetrahydrodesoxycodeine (II), identical with the corresponding compound derived from codeine.



This second article will discuss the analgesics obtained either by transformation of natural alkaloids or entirely by synthesis. The first group of partially synthetic analgesics will be dealt with separately from the group of compounds more recently prepared by total synthesis.

Since the chemical research which produced the analgesic compounds discussed in this review was undertaken in the hope of discovering analgesics free from the undesirable secondary actions of morphine, it will be necessary to preface the chemical part of this article with a very brief outline of the principal pharmacological properties of morphine, with particular emphasis on those side-effects which constitute the most serious clinical drawbacks.

Outline of the Pharmacology of Morphine

Morphine acts as an almost universal analgesic against pain in its various forms. When a large enough dose is administered, analgesia is usually followed by sleep.

* *United Nations Bulletin on Narcotics*, Vol. II, No. 2, page 8.

** Superior figures refer to the bibliography at the end of this article.

An earlier article by Paul Weill has treated of the chemistry of the natural analgesics, morphine and codeine, and has especially discussed the work that led to the elucidation of their molecular structure. The object of the present article is the chemistry of artificial analgesics, discussing first the substances obtained by chemical transformation of the natural alkaloids, and subsequently the totally synthetic drugs. The first of those groups obviously retains the essential carbon-nitrogen skeleton of morphine; among the totally synthetic analgesics, one group also contains this skeleton, while others have only remote chemical analogies with morphine.

This sequence is characteristic of morphine, whereas other types of medical preparations are either hypnotic but not analgesic (barbiturates) or antalgic but not hypnotic (salicylates).

The analgesic action of morphine is accompanied by numerous secondary effects, some of which are particularly objectionable. The worst of these are habituation and addiction, which increase rapidly with use. Much research has been inspired by the hope of separating those undesirable side-effects of morphine from its analgesic properties, but despite the large number of compounds prepared, only very limited success has been achieved. The recent discovery of synthetic products, a number of which have only a distant chemical relation to morphine, but which, like morphine, are both analgesic and habit-forming, would unfortunately appear to indicate that these properties are closely, and in all probability necessarily, inter-related.

The stimulation which morphine sometimes causes in human beings is regularly produced in certain animals like the cat. Thebaine produces this convulsive effect to such an extent even in man, that it may be regarded as a spastic poison, like strychnine. The respiratory centre is depressed by even small quantities of morphine, and the use of morphine in obstetrics is limited by the fact that minute doses produce this bulbar depression to a dangerous degree in the foetus and the new-born infant.

The action of morphine on the intestinal tract consists in lowering the tonus of the small intestine, and in causing constipation. In some cases it has a motor action on the stomach and a central emetic action. The latter property is predominant in the case of apomorphine.

Generally speaking, the morphine derivatives may be said to resemble morphine in their pharmacological properties. However, this analogy is only qualitative, since quantitatively they may differ considerably, not only with respect to the active doses, but also in the sequence and intensity of their effects. To the two examples already given, of thebaine and apomorphine, we shall add merely that of codeine, which is definitely inferior to morphine in its analgesic action, but which has no central depressive effect and is especially active as a cough sedative.

I

PARTIALLY SYNTHETIC ANALGESICS

In this section, those analgesics shall be discussed which are obtained from the natural alkaloids; since it is hardly feasible to mention every one of the numerous compounds prepared so far, only the more important and representative substances are considered.

We shall include under this heading, the analgesics obtained from the natural morphine alkaloids, but as we believe it to be unnecessary to refer to each one of the many compounds which have so far been prepared, we have confined ourselves to the most representative and important of them. The order of presentation follows no rigid system, since it was felt that any classification, whether chemical or pharmacological, was artificial and unimportant. Although this study is confined in principle to their chemistry, it appears essential to give a brief description of the main pharmacological and clinical characteristics of the compounds under consideration.

Diacetylmorphine

This alkaloid, commonly known as heroine, is obtained by the acetylation of the two hydroxyls of morphine. It is typical of the derivatives obtained by esterification of both the phenolic and alcoholic functions of morphine with various acids (propionic, valeric, benzoic, etc.).

Although its analgesic action is stronger and faster than that of morphine, heroine has only limited use because of its great drawbacks and dangerous features. It is more toxic than morphine, and very rapidly produces habituation and addiction, accompanied by intense euphoria and excitation. These latter effects make the heroine addict particularly dangerous. The manufacture and use of heroine are prohibited in many countries, including the United States.

Methylmorphine or Codeine, and Other Ethers of Morphine

Codeine (III) is produced when the phenolic hydrogen of morphine is replaced by a methyl group. It is present in opium but in quantities insufficient to meet the requirements of therapeutic practice. It is therefore prepared by methylation of morphine and we are including it among the partially synthesized derivatives. Codeine may be regarded as the first of a series of phenolic ethers of morphine, the most important of which are ethylmorphine or dionine, and benzylmorphine or peronine.

Inferior to morphine in its analgesic properties, codeine is also less toxic, while some of its undesirable secondary actions, such as the danger of addiction and the effect on the intestine, are much less pronounced. Codeine is used as an analgesic where the pain is not too severe, and especially as a cough sedative, because of its non-depressive action on the respiratory centre, a feature which makes it preferable to morphine.

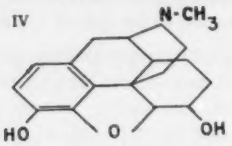
As an analgesic, *dionine* or ethylmorphine lies between morphine and codeine and is similar to the latter in its properties, particularly as a cough sedative. Its

action is regarded as superior to that of codeine, but is accompanied by greater toxicity. Dionine is sometimes used in ophthalmology because of its power to produce irritation and hyperaemia of the eye, desirable in certain cases.

Benzylmorphine or *peronine* is a more active but also a more toxic substitute for codeine.

Dihydromorphine or Paramorphan

IV



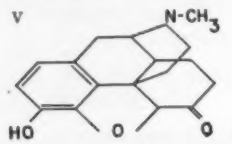
This compound (IV) results from the catalytic hydrogenation of the double bond of morphine in the presence of colloidal palladium. It is regarded as preferable to morphine, for which it is a substitute, by certain authorities who claim that it is a more powerful analgesic and less convulsive and toxic. It is not widely used, however; it has not been introduced in the United States and is hardly used any more in Europe.

Dihydrocodeine or Paracodine

Obtained by the hydrogenation of the double bond of codeine, this derivative has suffered the same fate as dihydromorphine.

Dihydromorphinone or Dilaudid

V



This compound (V), prepared by the Knoll Laboratories in 1926, results from the rearrangement of morphine under the action of catalysts like platinum or palladium, in the presence or absence of hydrogen.

Dilaudid has the advantage of being a more powerful analgesic than morphine, but this is counter-balanced by greater toxicity. While possessing the same general properties as morphine, dilaudid has a number of individual features which in some cases make it preferable to morphine: less habit-forming, according to some authorities; favourable action on post-operative intestinal spasms; less pronounced constipating and emetic action than morphine.

Dihydrocodeinone, Dicodid or Hycodan

This methyl ether of dilaudid may be prepared from codeine or thebaine. Under the influence of the same catalysts which transform morphine into dilaudid, codeine is similarly rearranged to give dihydrocodeinone. Thebaine (VI) also gives the same compound by the acid hydrolysis of dihydrothebaine (XIII) (*see p. 15*), its hydrogenation product.

A number of authorities ascribe to dihydrocodeinone properties which lie midway between those of morphine and codeine. Its most important feature is its activity as a cough sedative. The acetate of the enol form of dihydrocodeinone has been proposed in Germany as an antitussive under the name acedicon (XIV) (*see p. 15*).

Dihydro-hydroxycodeinone or Eucodal

This compound (VII) is produced by the catalytic hydrogenation of hydroxycodeinone (VIII), which is itself obtained by the action of hydrogen peroxide on thebaine (VI).

Eucodal, a substitute for morphine, lies midway between codeine and morphine in its action and is recommended as an analgesic. Of German origin, it is not used in the United States.

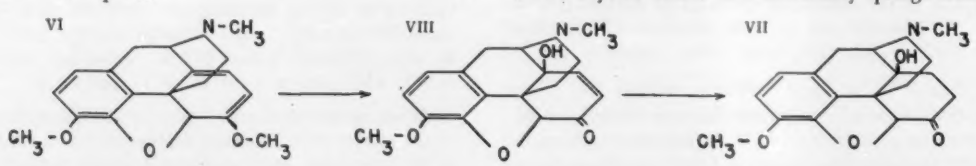
Dihydrodesoxymorphine D, Desomorphine or Permonid

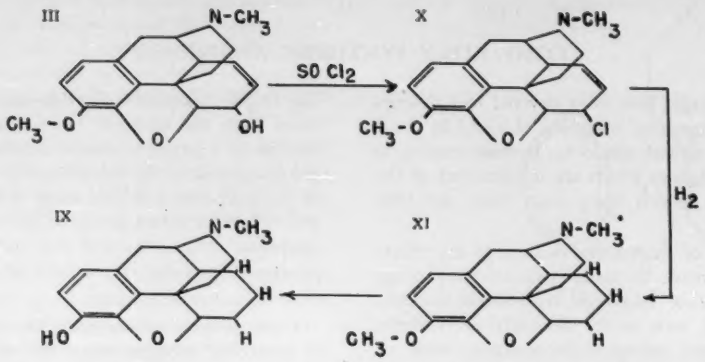
This compound (IX) was discovered by Small[3] in the course of his research on those derivatives of morphine and codeine in which oxygen is no longer attached to carbon atom 6. It is prepared from α-chlorocodide (X), which is itself obtained by the action of thionyl chloride on codeine (III). By catalytic reduction, α-chlorocodide (X) gives dihydrodesoxycodeine D (XI), which yields dihydrodesoxymorphine D on demethylation.

This substance appears to be remarkably active, with an analgesic effect about ten times greater than that of morphine; its toxicity, although likewise exceeding that of morphine, is apparently only three times as great. Its action is described as being very rapid but of short duration, and not accompanied by vomiting. It has been given the commercial name of permonid in Switzerland, where it is used.

Methyldihydromorphinone, Metopon

The constitution of this compound (XII), which was likewise discovered by Small[4], has not yet been established beyond doubt. This uncertainty springs from the





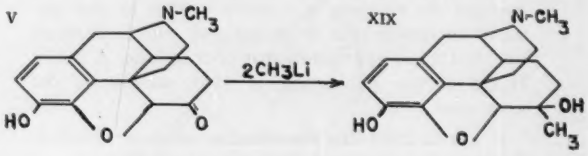
first reaction in the synthesis of metopon, the action of methyl-magnesium halide on dihydrothebaine (XIII), which is difficult to interpret for reasons discussed in the previous article.

The successive stages in the synthesis of methyl-dihydromorphinone are represented in the accompanying diagram taken from a recent publication by Small[5] on this subject. It will be noted that the first reaction mentioned actually produces two isomers, the manner of formation and constitution of which still defy satisfactory explanation.

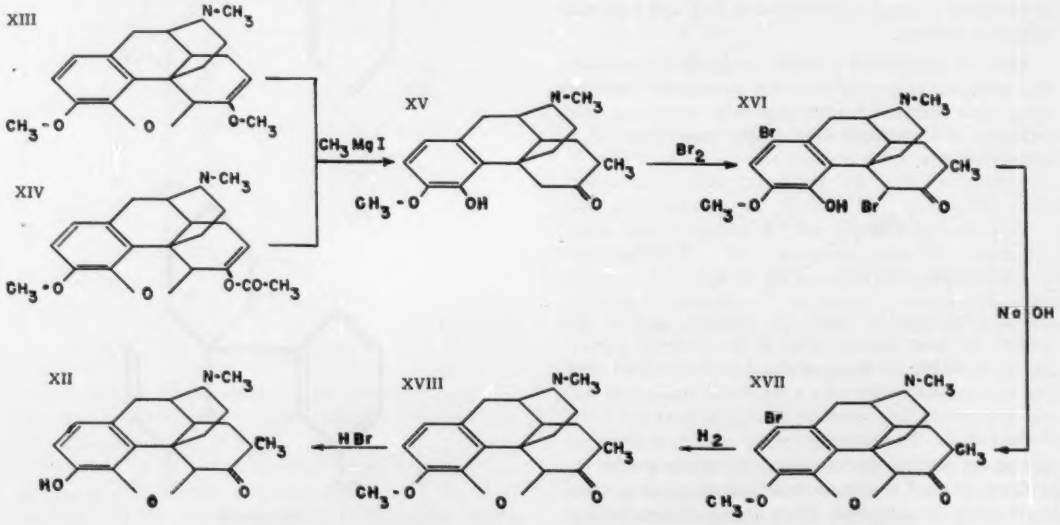
Metopon has been studied clinically only in cases of inoperable cancer. Its action has been ascertained by oral administration and it has been found to have few undesirable side-effects. The addiction to which it gives rise is less pronounced than that caused by morphine. Despite these promising indications, it would be premature to form any final judgment as to its value.

6-Methyldihydromorphine

Small and Rapoport[6] are responsible for discovering this product (XIX). They demonstrated that the keto-groups of dihydrocodeinone and dihydromorphinone (V), which are virtually inert to Grignard reagents,



react normally with methyl-lithium to produce the tertiary alcohols. 6-Methyldihydromorphine was obtained by the action of methyl-lithium upon dihydromorphinone. The most remarkable feature of this compound appears to be the duration of its analgesic action.



II

COMPLETELY SYNTHETIC ANALGESICS

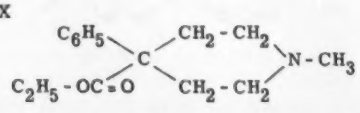
The preceding pages have been devoted to a description of the more important analgesics obtained by transformation of the natural alkaloids. It now remains to consider those analgesics which are independent of the natural bases and which have been made by total synthesis.

A large number of studies bear witness to the efforts which have been made to obtain pain-relieving drugs by complete synthesis. Although remarkable successes had been achieved, such as the discovery of synthetic local anesthetics and antalgics, no analgesic with an effect comparable to that of the opiates had been obtained by total synthesis until the last few years. "Only morphine and some of its derivatives can be regarded as true analgesics" wrote E. Fourneau in 1938, expressing the opinion of that day. It is true that the work, started in the United States in 1929 under the auspices of the National Research Council, directed by L. F. Small, included the synthesis of a certain number of true synthetic analgesics; but their analgesic effect, although real, had never approached that of morphine. A Public Health Service publication of 1941 summarizes the work done.[7]

It was in 1939 that the situation suddenly changed, thanks to the sensational discovery of pethidine (dolantin, demerol) (XX) in Germany by Eisleb and Schaumann.[8] The synthesis of pethidine was not due to *a priori* considerations regarding the relations between constitution and activity, or to systematic research work on analgesics. It was achieved during work on antispasmodics, and the discovery of its analgesic effect was the result of a happy combination of luck and a pharmacologist's acumen.

This first completely synthetic analgesic demonstrated that analgesic properties were not necessarily dependent on a close chemical relationship with morphine, since pethidine is a comparatively simple phenyl-piperidine-carboxylic ester.

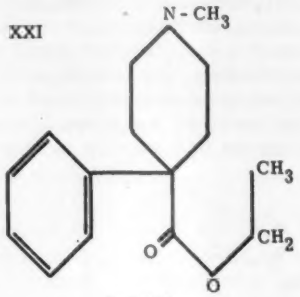
XX



The experiments, which in number, quality and method are most representative of the tendency prevailing up to 1939, are those of the American school. Carried on simultaneously with a structural analysis of natural analgesics, they seem necessarily to bear the traces of their origin. They show a certain concern to duplicate part of the natural models, apparent in the special importance attached to certain structural elements or functional groups of morphine. Thus, amino-alcohols belonging to the phenanthrene, dibenzofuran and carbazole series were the favourite themes, varied by the introduction of a larger or smaller number of the functional groups present in the natural analgesics. The complexity of the morphine molecule stood in the way of a speedy and systematic investigation of the value of the various morphinic fragments, and the uncertainty which still persisted regarding its constitution was an additional obstacle.

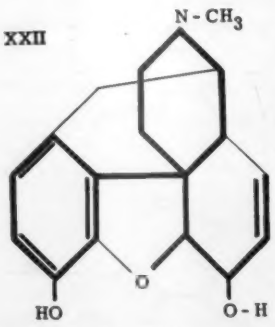
It was in these circumstances that the chance discovery of pethidine brought about the revolution which released the imagination of chemists and opened new approaches to the problem. This revolution was marked by a remarkable simplification of the concepts hitherto accepted, the verification of which would have taken many years longer, and by the importance which was suddenly assumed by some parts of the morphine molecule considered less essential before. Schaumann realized only afterwards that the structure of pethidine could be related to that of morphine, if a special way of writing the two molecules was adopted. The formulations XXI and XXII are taken from Yonkman.[9]

XXI



Pethidine

XXII



Morphine

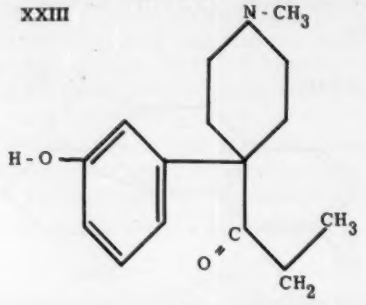
This relationship revived the interest of chemists in the study of synthetic analgesics, and thus opened up a whole unsuspected field of research. Its exploitation, which has been vigorously carried forward since the original discovery, has already produced such an ample harvest that only a brief summary of the work accomplished can be given. Excellent reviews like those of Bergel and Morrison,[10] some articles in the Barell Jubilee volume[11] or those of N. Eddy[12] and Wolff,[13] and the monograph of the New York Academy of Sciences[14] are available.

The work set in motion by the discovery of pethidine was directed at first quite naturally toward the exploitation of the initial success. Changes in the respective positions of the functional groups, modifications or displacement of subsituents, and the preparation of derivatives from the original molecule, were, and still are, important themes of research.

The articles referred to above give an account of the progress achieved in this direction and draw such conclusions as are possible regarding the new relations which appear between chemical composition and pharmacological activity. Those of Foster and Carman[15] and Eddy[12] are particularly instructive in this respect, and make a detailed discussion in this summary unnecessary.

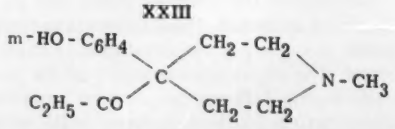
Among all the derivatives prepared in the pethidine series, we shall confine our attention in this general statement to "keto-bemidone" (XXIII), which results

XXIII



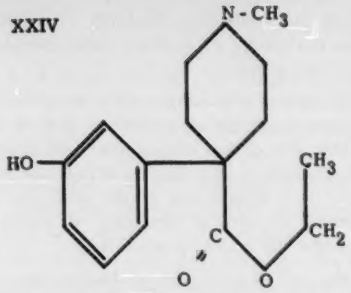
or

XXIII



from a double modification of the pethidine molecule. The first consists of the introduction of a hydroxyl into the meta-position of the phenyl nucleus and produces bemidone (XXIV), the activity of which is comparable to that of the original molecule. The second modification replaces the carbethoxy group of bemidone by the

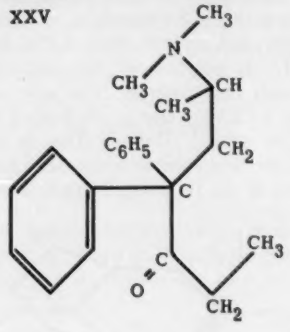
XXIV



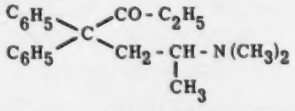
ketonic grouping, -CO-C_2H_5, which increases the activity of the compound ten-fold.

The considerable activity of such a ketone obviously opened the way for a new series of completely synthetic analgesics, the chief of which is methadone (XXV). This compound, which, like keto-bemidone, was discovered by the I. G. research staff during the war, has the following formula.

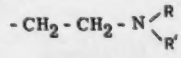
XXV



or



We recognize here the ketonic group -CO-C_2H_5 which is present in keto-bemidone and which makes this compound the bridge connecting the pethidine series with the methadone series. Nevertheless, methadone differs from keto-bemidone by the aliphatic character of its amino-nitrogen. The departure from the heterocyclic series is the result of the exploration by Bockmuehl and Ehrhart[16] of a series of compounds containing the group below, instead of the piperidine nucleus; some of those



compounds show both anti-spasmodic and analgesic effects. Methadone is therefore reminiscent of two previous discoveries, one demonstrating the importance of the ketonic function, which is foreign to natural anal-

gesics, and the other the possibility of replacing the piperidine nucleus by an aliphatic chain carrying a substituted amino group.

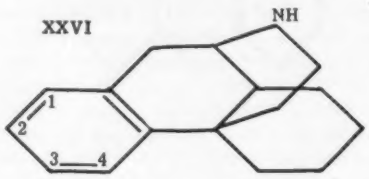
The analogy of methadone with morphine is even more remote than that of pethidine. Yet its formula, given above, brings out certain points of resemblance. These are confirmed, according to Bergel and Morrison, (loc. cit.) by a comparison of the molecular models, which shows the spatial similarity of methadone to morphine and the phenyl-piperidines.

As in the case of pethidine, methadone was the starting point for a vast amount of research on related compounds, which are reviewed in the article by Eddy (loc. cit.; especially Table III, page 249).

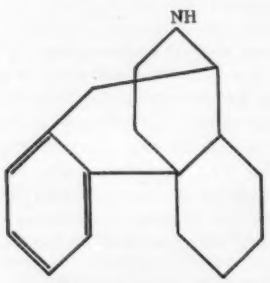
Before leaving the methadone series in these general remarks, let us note that no noticeable increase in its activity has been obtained by the modifications made in its molecule, except by optical resolution.

The two series which we have passed in rapid review were only attached to the morphine series by *a postieri* considerations, and do not even derive from it historically. This is not true of the morphinane series, which we shall now consider. The very name of the first product (XXVI), clearly emphasizes its relationship with the natural alkaloids. This is no longer a fragment of the morphine structure, but rather its complete skeleton as the following formula shows:

XXVI



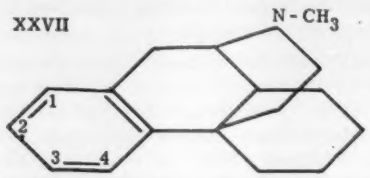
or



Morphinane

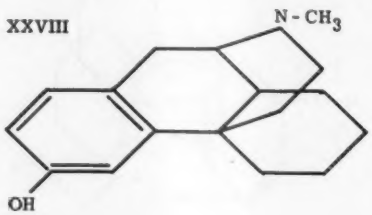
The brilliant successes so rapidly achieved in this series are due chiefly to Grewe[17]; the synthesis of morphinane marks the first memorable stage of this work. Other authors had attacked the problem of the synthesis of compounds containing the complete morphine skeleton in the hope of preparing the way for the synthesis of morphine. The review of Bergel and Morrison gives an account of these experiments, prior to those of Grewe. Their interest is now mainly historical. The work of Grewe and his associates or competitors will be discussed later in a special chapter. Up to now, its culminating point has been the synthesis of the l-isomer of tetrahydrodesoxycodeine (II), which constitutes the first example of the synthesis of a compound identical with a derivative of a natural analgesic still possessing the complete skeleton of morphine. Grewe's success is not only outstanding in the chemical field, it far transcends it, by throwing new light on the relations between the structure and the activity of analgesics. Thus N-methyl-morphinane (XXVII), without possessing the

XXVII



oxygen bridge, the hydroxyls or the double bond of morphine, has proven, contrary to all expectations, to have an undeniable analgesic effect, which is strengthened and prolonged by the simple introduction into position 3 of a hydroxyl, analogous to the phenolic group of morphine, to such an extent that 3-hydroxy-N-methyl-morphinane (XXVIII) becomes a rival to morphine.

XXVIII



It would appear that a comparative examination of the natural, and the partially or completely synthetic analgesics ought to show clearly to what structural or functional characteristics the analgesic power and its properties should be attributed. These lessons, however, have been neither as numerous nor as valuable as might have been hoped. The stereochemical aspect of the problem of the relationship between the chemical structure and the analgesic activity has been discussed in the review of Bergel and Morrison. To enter into it here would exceed the limits of this article without adding anything to the excellent account of the English authors. We shall therefore content ourselves with reproducing the conclusions of N. B. Eddy at the end of his 1950 paper which sums up our present knowledge:

1. The presence of a tertiary amino-nitrogen seems to be essential in an analgesic compound. This nitrogen may be part of a heterocycle (piperidine, tetrahydroquinoline, morpholine, pyrrole . . .) or of an open chain.

2. The presence of a quaternary carbon linked through -C-C- with the amino-nitrogen has been noted hitherto in analgesics in the morphine, pethidine and methadone series. Its presence, and the relationship to nitrogen described above, might not be absolutely necessary, but at least they seem to be responsible for the maximum intensity of the analgesic effect.

3. Certain substitutions of functional groups for others, listed in Eddy's article, produce changes of the same type and of the same extent if carried out in the different analgesic series.

4. The toxicity and the analgesic effect are not necessarily affected to the same extent or in the same way by the various modifications described.

5. Unfortunately, no analgesic has been obtained which does not induce habituation and addiction.

The three series of completely synthetic analgesics considered so far, the pethidine, methadone and morphinane series, do not include all the analgesics discovered in the course of recent research. A number of these are not covered by any systematic classification. We shall therefore have to consider them in a separate group.

Leaving now this chapter of general considerations, intended to facilitate the understanding of the following chapters which are devoted to the chemistry of the various series of completely synthetic analgesics, we shall abandon the chronological order to adopt one which is more logical from the chemical point of view. We shall begin with the morphinane series, which has the same fundamental structure as the partially synthetic analgesics. There will thus be a more natural transition to the pethidine and methadone series, the relationship of which to the natural analgesics is becoming increasingly remote. The synthetic compounds which do not fall easily into any classification will be examined at the end.

The importance attributed to the various series will not be the same. It is our belief that it is of little interest to paraphrase or recapitulate the excellent articles which have already appeared and to which we have referred above. The morphinane series is the only one which apparently has not yet been the subject of a review, and will therefore be discussed in greater detail than the rest.

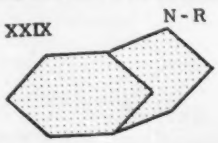
Morphinane Series

The first group of synthetic substances to be discussed consists of those which possess the same carbon-nitrogen skeleton as morphine itself. The synthesis of such structures was first achieved by Grewe in 1946.[17] Before describing this work, however, it may be interesting to mention a few forerunners.

A number of authors have synthesized compounds which duplicate only certain characteristic parts of the morphine skeleton rather than the entire structure.

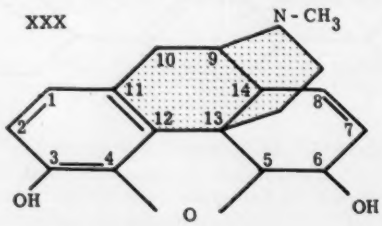
Since the ring system, 2-azabicyclo-[3,3,1]-nonane

XXIX



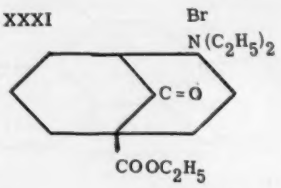
(XXIX, R=H), is present in the formula of morphine

XXX

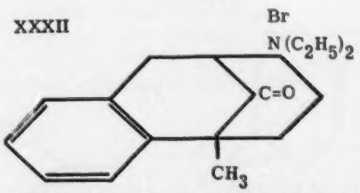


(XXX), the name "morphan" was proposed for the above structure by Barltrop,[18] who describes the synthesis of some of its derivatives, such as XXXI and XXXII.

XXXI

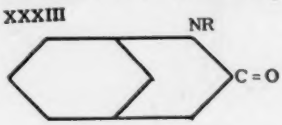


XXXII



Subsequently, Cronyn[19] and Ginsburg[20] obtained morphan itself and its N-ethyl derivative (XXIX, R=C_2H_5) through reduction of the corresponding lactams (XXXIII). The lactams had a certain analgesic activity,

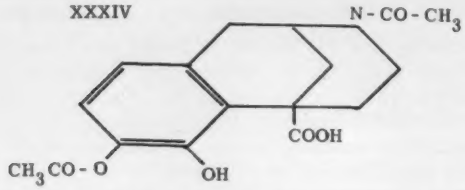
XXXIII



while morphan itself and its N-ethyl derivative were inactive.

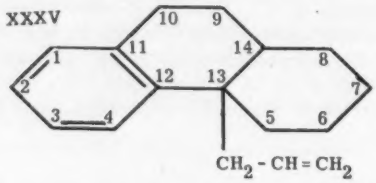
Related compounds such as XXXIV were prepared by Horning and Schock.[21]

XXXIV

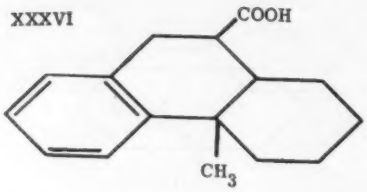


Attempts in another direction aimed at synthesis of the partially hydrogenated phenanthrene system with a substituent in position 13.[22] Similar compounds were prepared by Grewe[23] at earlier stages of the work that later culminated in the synthesis of substances containing the entire C-N skeleton of morphine. Compounds such as XXXV and XXXVI were obtained, but attempts to prepare XXXVII led to XXXVIII instead. This cyclization to a substance with a ring system similar to that of morphine itself induced Grewe to investigate the cyclization of heterocyclic systems analogous to XXXVII.

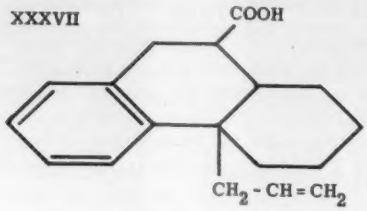
XXXV



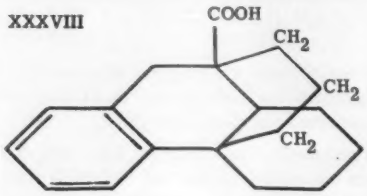
XXXVI



XXXVII



XXXVIII



A comparatively simple synthesis of 5, 6, 7, 8-tetrahydro-isoquinoline (XXXIX) was worked out (see Chart I); this compound was further transformed to the desired N-methyl-1-benzyl-octahydro-isoquinoline (XL) in the manner shown in Chart I, if Ar=C_6H_5. The formula of this last compound can be rewritten in such a way that its relationship to the morphine type of structure becomes readily apparent. Although the required cyclization to XXVII, N-methylmorphinane, seems without a close analogy, it proceeded smoothly on heating XL with concentrated phosphoric acid to 150°, yields better than 50 per cent of XXVII being obtained, together with smaller quantities of two by-products, one of which is identical with a compound recently synthesized by an entirely different route.

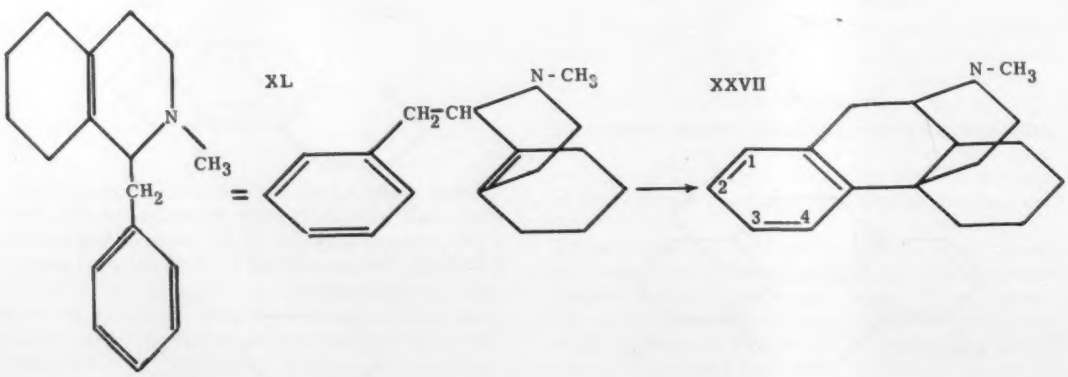
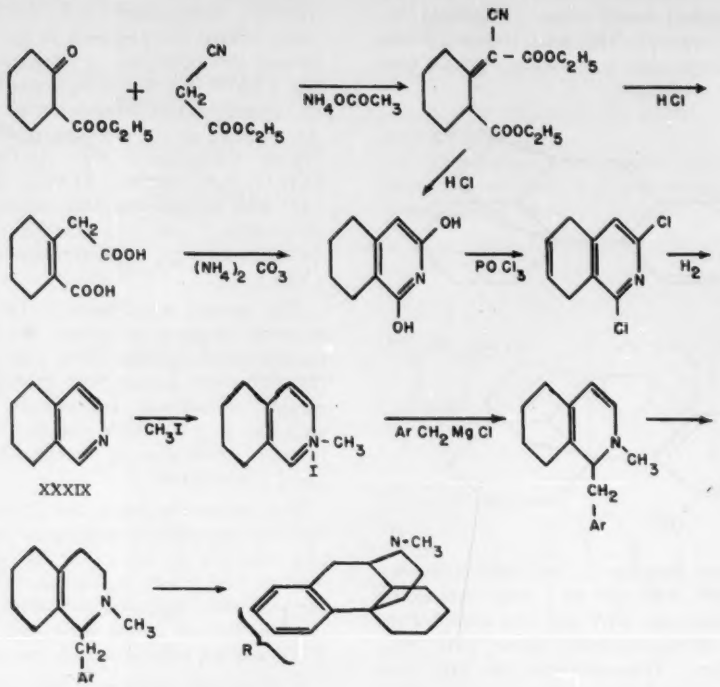
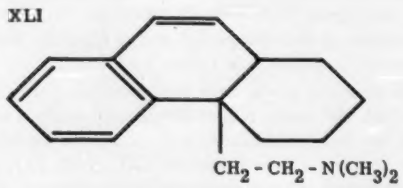


Chart I



Grewe proposed the name "N-methyl-morphinane" for the main product (XXVII) of this brilliant synthesis; its structure was proved by exhaustive methylation to the des-base XLI, which was readily converted to phenanthrene by heating with Pd-charcoal, and reduced catalytically to a dihydro derivative identical with a compound prepared by an independent synthesis.

XLI

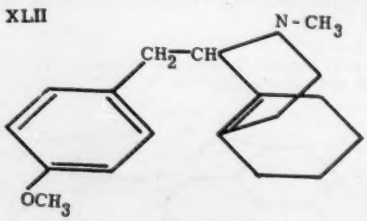


Action of BrCN on N-methylmorphinane yielded the parent compound of the whole series, morphinane (XXVI).

On pharmacological investigation, N-methylmorphinane showed pronounced analgesic activity, a very surprising property for a compound of morphine-like structure lacking the oxygen bridge.

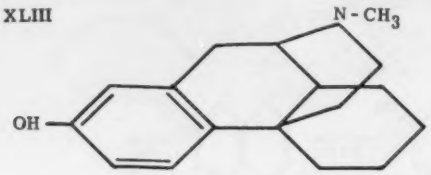
This analgesic activity is much more pronounced in 3-hydroxy-N-methylmorphinane (XXVIII), which was obtained by Grewe, Mondon and Nolte[2] and by Schnider and Grüssner[24] through cyclization of the compound XLII and demethylation (Grewe *et al.* achieved both reactions in one step by heating with concentrated HBr). The Swiss authors[24] also prepared 3-hydroxy-N-methylmorphinane by nitration of N-methylmorphinane and subsequent reduction and diazotization. The high, rather long-lasting analgesic activity of this compound (also referred to as morphinan, dromoran and NU 2206) has led to its thorough pharmacological and clinical investigation.

XLII

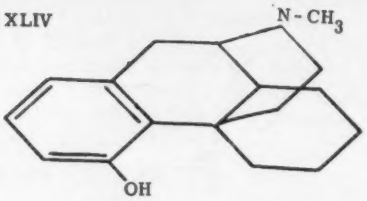


Schnider and Grüssner (loc. cit.) also prepared 2- (or 4-) hydroxy-N-methylmorphinane (XLIII or XLIV; it was not established which isomer is formed), but found it entirely inactive. The same is true of compounds of the morphinane series having groups other than methyl on the nitrogen.

XLIII



XLIV



Further important progress in this field is due to Grewe, Mondon and Nolte (loc. cit.), who succeeded in synthesizing the compound XLV and who identified its levo-isomer with tetrahydro-desoxycodeine (II) prepared from codeine.* This constitutes the first total synthesis of any compound of the morphine series which is also accessible through transformation of the natural alkaloids by methods which presumably do not alter the fundamental ring system. The identity of the synthetic substance with the one derived from codeine provides very strong support for Gulland and Robinson's morphine formula (I).

For the synthesis of compound XLV, the route utilized in the synthesis of N-methylmorphinane could not be used, since the required compound Ar-CH_2-MgHal with Ar=3, 4-$(CH_3O)_2C_6H_3$- is not accessible; the authors therefore attempted first to start with N-methylmorphinane (XXVII) itself, trying to introduce a halogen atom into position 4, which was to be exchanged subsequently for an OH group. However, it was found that halogen invariably enters position 2 first, 2, 3-dihydroxy-N-methylmorphinane being finally obtained.

A new sequence of reactions had therefore to be worked out (See Chart II). Following this general method, morphinane and 3-hydroxy-N-methylmorphinane were first prepared. In the first case, the intermediate chlorobenzylate of 1-benzyl-tetrahydro-isoquinoline (XLVI, R=Ar=C_6H_5) was reduced catalytically to 1-benzyl-octahydro-isoquinoline (XLVII, R=H, Ar=C_6H_5), which was then cyclized to morphinane. Finally, the synthesis with R=CH_3 and Ar=3, 4-$(CH_3O)_2C_6H_3$- yielded XLVIII. This, on heating to 130° with concentrated HCl, underwent demethylation in position 4 and cyclization simultaneously to give the desired 4-hydroxy-3-methoxy-N-methylmorphinane (XLV).

This product was shown to be identical with the racemate obtained by mixing the l- and d-forms of tetrahydrodesoxycodeine (II), prepared by a series of transformations starting with natural codeine and sinomenine, respectively. Furthermore, resolution of the synthetic racemate XLV via the tartrate yielded the l-isomer, identical with l-tetrahydrodesoxycodeine prepared from codeine.

It is remarkable that in the cyclization of N-methyl-dimethoxybenzyloctahydro-isoquinoline the alternative ring closure to the 2, 3-substituted morphinane does not seem to take place; it does so, however—at least in part—if more strenuous conditions are used for the reaction. Because of its sensitivity, the resulting base XLIX was not isolated as such, but as its dimethylether.

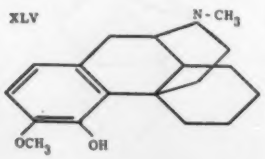
It is equally remarkable that among the possible diastereomers of XLV only the one corresponding in its configuration to the natural alkaloids has been obtained. However, as has already been mentioned on page 20, this does not apply to the synthesis of N-methylmorphinane, where two isomers of the main product were produced together with the latter. That one of them is actually a stereoisomer of N-methylmorphinane is shown by the recent work of Gates and co-workers.[25]

These authors carried out the sequence of reactions outlined in chart III; they found that the final product (L), an isomer of N-methylmorphinane, has the same constitution as this compound and is identical with one of the two by-products in Grewe's synthesis.

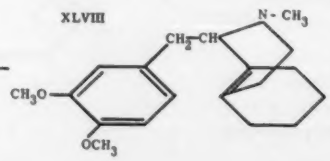
The structure of the base synthesized by Gates *et al.*, for which the name N-methyl-isomorphinane was proposed, has been established by its exhaustive methylation to the des-base, a stereoisomer of XLI (*see p. 23*), which was converted to 1,2,3,4-tetrahydrophenanthrene on distillation with zinc dust.

* *United Nations Bulletin on Narcotics*, Vol. II, No. 2, page 19, and page 12, this issue.

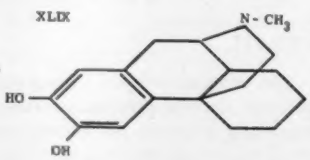
XLV



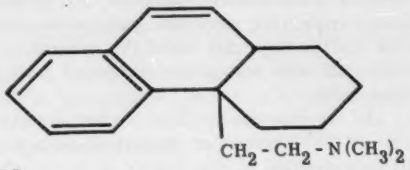
XLVIII



XLIX



It is stated by Gates *et al.* that N-methyl-isomorphinane shows considerable analgesic activity in animal tests.



XLI

Addendum

Since the completion of the manuscript of this article, several papers in the field of morphinane and its derivatives have appeared, which should be mentioned briefly.

1. A short review of this subject by A. Mondon has become available.[26]

2. Two United States patents[27] cover the synthesis of N-methylmorphinane and describe many derivatives and related compounds.

Chart II

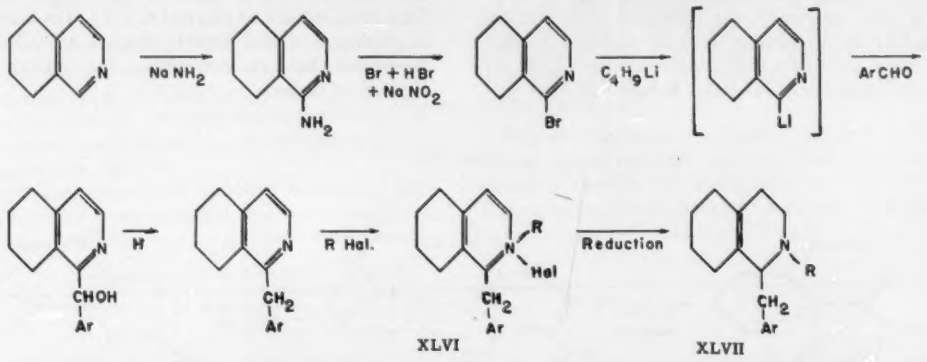
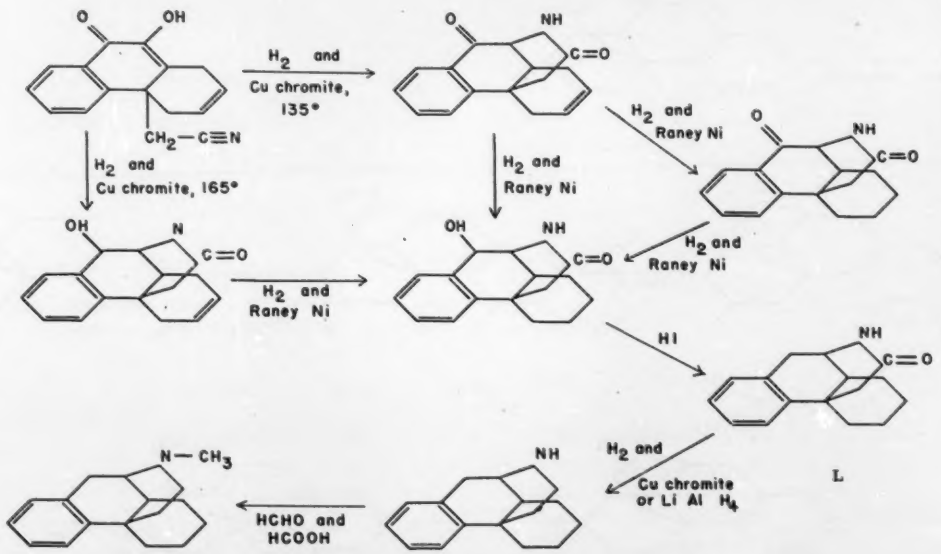


Chart III



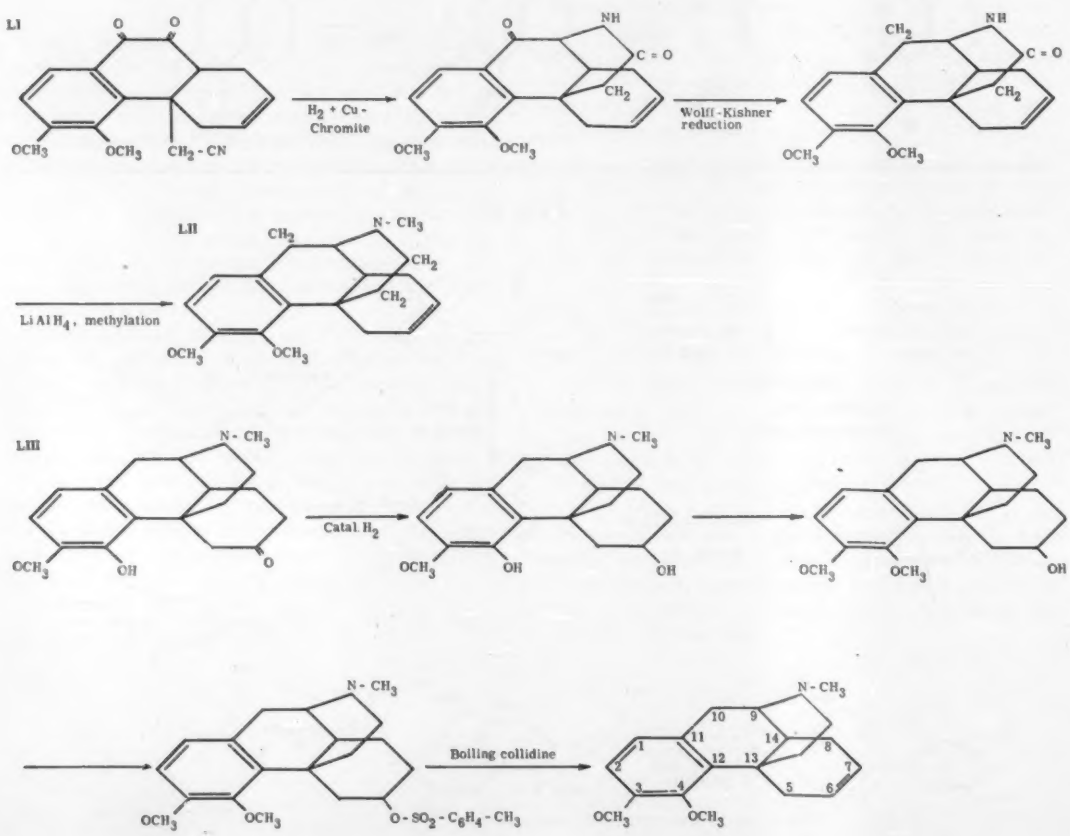
A This formula also represents compound L.

3. Schnider and Hellerbach[28] give a new synthesis of 1-benzyl-octahydroisoquinolines (XL) which does not require the use of benzyl-magnesium halides. This route is therefore well adapted to the preparation of such compounds of type XL, which could not be made by the original procedure of Grewe because of the impossibility of preparing the required Grignard reagents. By cyclization of their benzyl-octahydroisoquinolines, Schnider and Hellerbach obtained several new derivatives of morphinane, including d,l-tetrahydrodesoxycodeine.

4. Gates and Tschudi[29] made important progress in the isomorphinane series. They succeeded in cyclizing LI in a way analogous to that formulated in chart IV for the corresponding methoxyl-free substance, and in converting the reaction product in several steps into LII. This racemic compound was compared with material prepared by the sequence of reactions outlined in chart IV, starting with either dihydrothebainone (LIII) or β-dihydrothebainone. This latter ketone had been prepared by Small and Browning[30] and formulated as the epimer of LIII with opposite configuration at C-14. Gates and Tschudi compared the optically active products derived from dihydrothebainone and β-dihydrothebainone respectively with the synthetic racemate by infra-red spectroscopy, and found the spectrum of LII to be identical with that of the compound from β-dihydrothebainone.

This identity provides excellent support for the correctness of the structure of N-methyl-isomorphinane, and its interpretation as the epimer of N-methyl-morphinane. Beyond that, the fact that the product of LII of a cyclization of the C-13-substituted phenanthrene LI has been found identical with a derivative of natural codeine, shows that in the latter the nitrogen-containing chain must equally be attached to C-13. The unequivocal establishment of this point by degradative methods had constituted the main difficulty in the research on the structure of codeine.

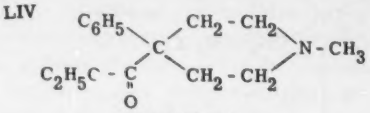
Chart IV



The history of the synthesis of pethidine, and of the discovery of its analgesic properties by Eisleb and Schaumann[8] has been related above.

Pethidine was originally named "dolantin" and is also known under the synonyms demerol, dolantal, meperidine, isonipecaine, etc. It is the ethyl ester of N-methyl-4-phenyl-piperidine-4-carboxylic acid. Its chemical formula can be written as LIV, or LV (in Chart V).

LIV



[*Pethidine*]

Pethidine was first synthesized by the condensation of benzyl cyanide with N-methyl-β, β'-dichloro-diethylamine in the presence of sodamide, saponification of the nitrile group and esterification of the carboxylic acid thus obtained. See chart V.

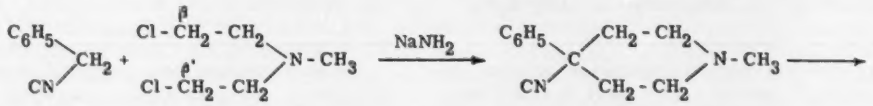
Several other methods of synthesis have been suggested since then; their principal aim was to avoid the use of the powerful vesicant, N-methyl-dichloro-dimethylamine. The German method which was made public after the war, and which was described in American and British technical reports[31] on captured documents, uses the less-dangerous N-benzyl-β, β'-dichlorodiethylamine. The substitution of methyl for benzyl then takes place during a final reaction which utilizes reduction by hydrogen in the presence of palladium and formaldehyde. Chart VI illustrates that method, which has an overall yield of about 25 per cent.

Two other methods successfully used by Bergel and his collaborators[32] and by Walton and Green[33] are illustrated in chart VII (*see p. 26*).

Of the other proposed methods of synthesis, we shall only mention one for which Ciba holds a British patent[34] and in which pethidine is obtained through the hydrogenolysis of a quaternary ammonium salt (Chart VIII) (*see p. 26*).

Recently, radioactive pethidine, labelled in the N-methyl group, has been prepared. This compound was obtained through the methylation of 4-phenyl-4-carbethoxypiperidine by means of a mixture of radioactive formaldehyde and formic acid.[35]

Chart V



LV

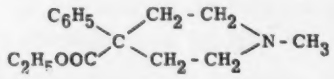


Chart VI

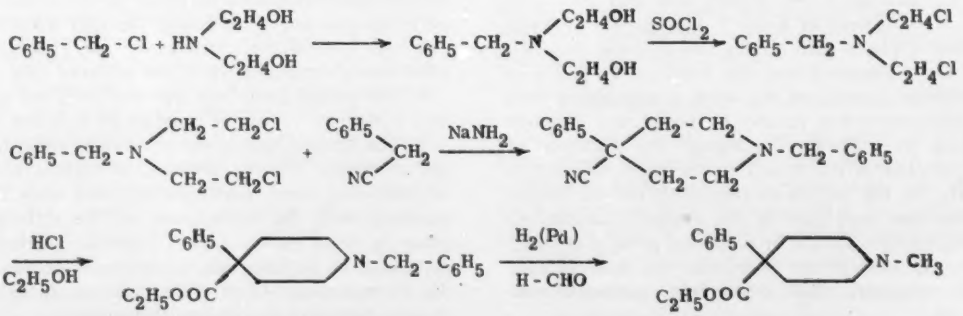
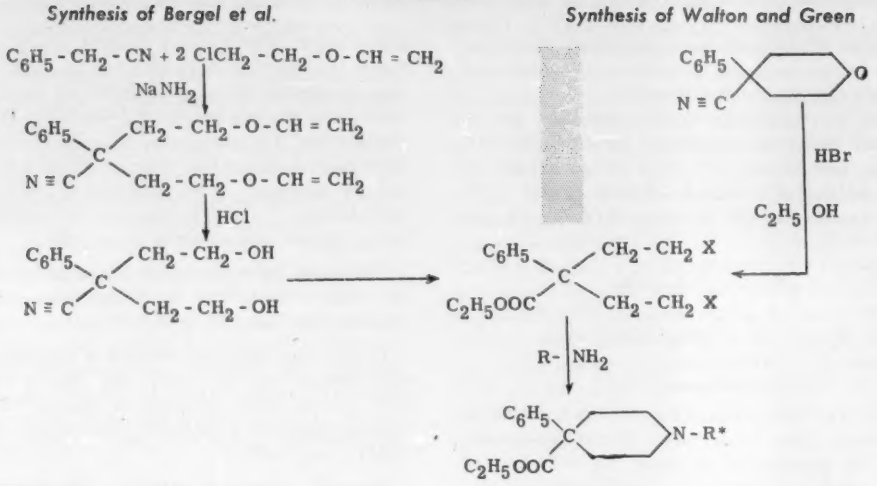


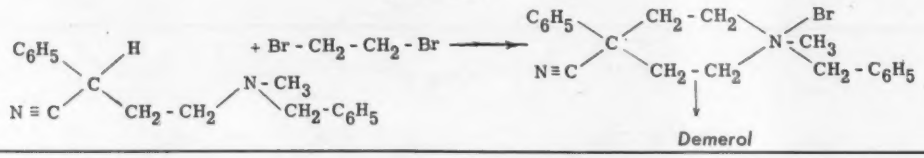
Chart VII



* R is CH_3 in the case of pethidine.

Chart VIII

[*Pethidine*]



The physical and chemical properties of pethidine are not of sufficiently general interest to be described here. The pharmacology of pethidine has been described by Yonkman in an article published in 1948.[9] Although pethidine is a less powerful analgesic than morphine, it has the advantage of not depressing the respiratory center; it is therefore valuable in obstetrics. The initial belief that pethidine is not habit-forming has not been confirmed by subsequent observations.

The discovery of pethidine was rapidly exploited. As early as 1940 Schaumann himself[36] was able to report on pharmacological tests dealing with over forty compounds synthesized by Eisleb.[37] Various other research workers displayed such activity that by 1948 the pethidine series comprised over 200 members. To give even a condensed account of this work is unnecessary since the above-mentioned reviews by Bergel and Morrison or Eddy are available. To conclude this discussion of the pethidine series, it will be therefore sufficient to classify not the derivatives themselves but the various modifications undergone by the original molecule, according to the molecular or functional group they affect. Evidently, some of the transformations were brought about separately, while others were combined with each other.

We shall examine three groups of modifications of pethidine according to whether they affect the benzene ring, the piperidine ring or the ester function, each of them comprising a few sub-divisions.

Benzene Nucleus

1. Various substituents were introduced into different positions; for instance, one methyl in the ortho position; a hydroxyl, free, etherified or esterified, in the meta or para position. Bemidone (XXIV) is among the derivatives of this group, the synthesis of which sets out from m-methoxybenzyl cyanide according to the method used in the preparation of pethidine; the only difference is that hydrolysis of the nitrile group and demethylation are achieved simultaneously by the action of HBr.

2. The phenyl group was separated from the quaternary piperidinic carbon by insertion of a carbon chain.

3. The benzene nucleus was replaced by either hydrogen or various aliphatic, aromatic or alicyclic radicals. In most cases, these transformations were made simultaneously with the replacement of the carboxyester group by esters derived from a piperidinic carbinol in position 4. In the latter case, the synthesis sets out from the corresponding 4-piperidone, utilizing $LiAlH_4$, or organo-magnesium or -lithium compounds.

Piperidine Ring

1. The methyl attached to the nitrogen was replaced by other radicals. Its replacement by butyl, accompanied by the change from the carboxylic series to the carbinolic series, with esterification by propionic acid, increases the analgesic activity.

2. The respective positions of piperidine nitrogen and quaternary carbon were modified. The series with the quaternary carbon in the 3 rather than in the 4 position is generally known as the iso or β series. The carbon having become asymmetric, the synthetic racemate may now be resolved into two enantiomorphs, the more active of which is the levorotatory isomer.

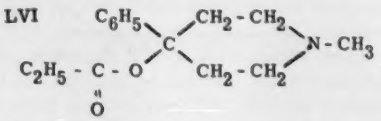
3. The addition of substituents to the piperidine ring made it possible to show that the activity is increased by the presence of a methyl in position 3.

Ethyl Carboxylate Function—$COOC_2H_5$

1. The ethyl radical was replaced by numerous other radicals. Such changes usually produced a considerable decrease in analgesic activity, except in a few rare cases (isopropyl, allyl, n-propyl).

2. The carboxylic group was replaced by a hydroxyl. The carbinol thus obtained was acylated by various acids. Propionic acid led to the most active compound of the series (LVI), about five times more active than pethidine itself.

LVI



3. The oxethyl part of the ethyl carboxylate group was replaced by various radicals, thus giving rise to the ketonic series; its most important representative, keto-bemidone (XXIII) (*p. 17*) has already been mentioned. Replacement by $-NH_2$ was also tried; the resulting amides were active.

4. The carboxyl group was shifted from its position 4 on the piperidine ring, with loss in activity.

5. The carboxyl group was replaced by hydrogen or certain radicals such as phenyl, or even by a sulfone group.

* * *

Certain transformations of the pethidine molecule affect several of its functional groups; some examples, such as keto-bemidone, have already been mentioned in this paper.

Methadone Series

Methadone (LVII, in Chart IX) resulted from research in the laboratories of I. G. Farbenindustrie A.G. at Hoechst-am-Main, Germany. It was referred to as compound 10820, or amidone; its value, apparently not quite appreciated by its discoverers, became known through reports of Allied investigators.[38] The powerful analgesic action of the compound has led to great interest in its pharmacology; it has been introduced into medical use in the United States under the name "methadone", in England as "amidone." Other names used for this product are: dolophine, adanone, physeptone, polamidone, AN-149, etc.

D,l-methadone is stated to be a stronger analgesic, weight by weight, than morphine, and to resemble it in most respects, unfortunately also in addiction liability; certain pharmacological differences, however, have been found. From the very extensive literature on the pharmacology of methadone, only a few leading references can be given here: Chen, *Annals of the New York Academy of Sciences, 51,* 83 (1948); Eddy, Touchberry and Lieberman, *Journal of Pharmacology and Experimental Therapeutics, 98,* 121 (1950); Denton and Beecher, *Journal of the American Medical Association, 141,* 1146 (1949).

The synthesis of methadone proceeds by the steps shown in Chart IX, leading finally to the two end-products, methadone and isomethadone (LVIII).

The chemistry of the reactions involved has been the object of much study; the rearrangement occurring in the synthesis of methadone is generally explained by assumption of reaction of the chloro-amine (LIX) in the cyclic form indicated in the flow sheet. The constitution of the various compounds has been demonstrated by degradative reactions and partly by independent syntheses.[39]

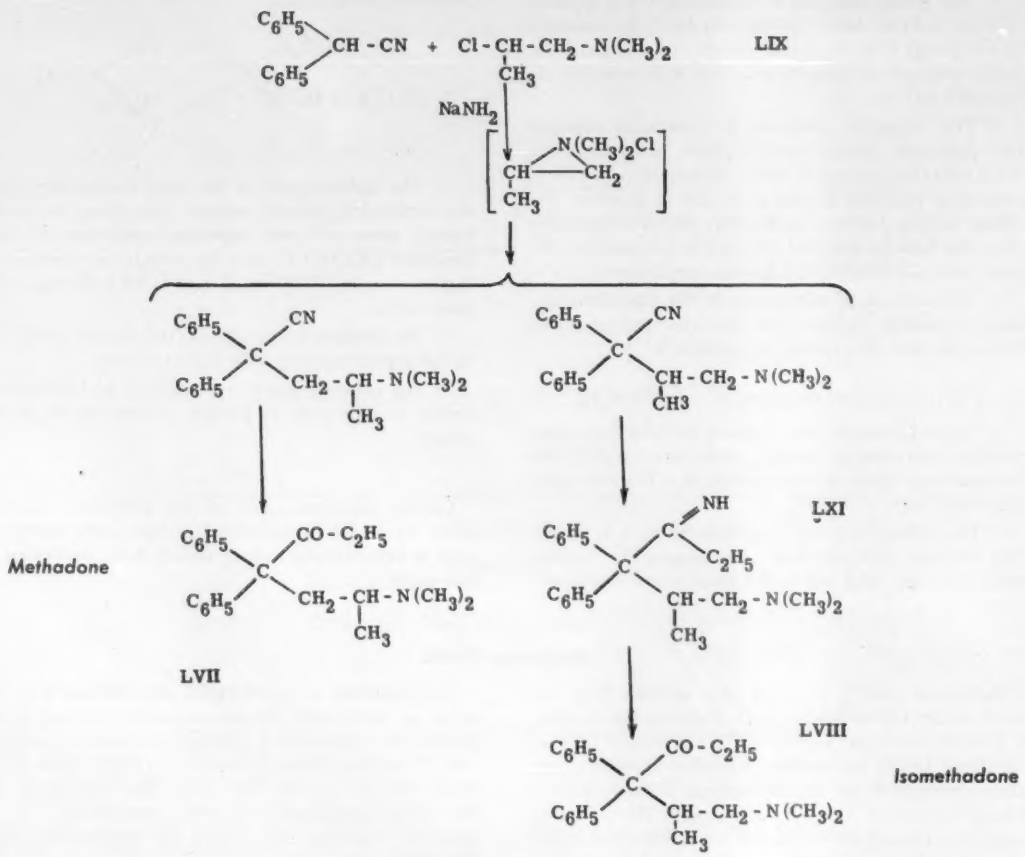
The resolution of the racemate, methadone, into the antipodes has apparently been studied in Germany. It has subsequently been achieved by several groups of workers: Thorp, Walton and Ofner,[40] Brode and Hill,[41] Larsen, Tullar, Elpern and Buck,[42] Howe and Sletzinger.[43] Comparison of the activity of the antipodes by several authors has shown that the l-isomers of methadone and isomethadone are much more potent analgesics than the d-isomers.[44]

Compounds related to Methadone

As was the case with pethidine, the success of methadone led to intense study of many chemically related compounds; only a few of the more important results can be mentioned here. The variations of the basic structure can be logically divided into the following groups:

1. Modifications of the aromatic rings.
2. Modifications of the nitrogen-containing side chain.
3. Modifications of the ketonic side-chain.

Chart IX



For more extensive discussions of the changes made, and the regularities found, see the articles by Chen and Eddy (loc. cit.).

1. *Modifications of the aromatic rings*

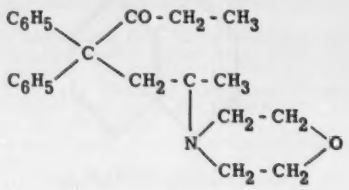
The introduction of substituents into the aromatic rings, or their replacement by other cyclic structures, led to diminution or disappearance of analgesic activity. Already the workers at Hoechst made the unexpected observation that introduction of one meta-OH group into a compound of the methadone series yielded a product having only a fraction of the activity of the parent substance; this is in striking contrast to the high activity resulting from the analogous change in the molecule of pethidine to give keto bemidone (XXIII), and of N-methyl-morphinane to give 3-hydroxy-N-methyl-morphinane (XXVIII).

2. *Modifications of the N-containing part of the methadone molecule*

Many compounds belonging to this class have been studied already by workers at Hoechst; their result that isomethadone (LVIII, in Chart IX) was relatively weakly active has more recently been contradicted.[45] Chen (loc. cit.) states that it is about half as potent as methadone. Eddy, Touchberry and Lieberman (loc. cit.) find it both less analgesic and less toxic than methadone, again the l-isomer being the active one; they state that parallel changes in the structures of methadone and isomethadone result in parallel modifications of activity.

Replacement of the $-N(CH_3)_2$ group in methadone and isomethadone by other nitrogen-containing residues has been extensively studied; especially morpholino- and piperidino- compounds have evoked much interest. The compound, d-l,-6-morpholino-4,4-diphenyl-3-heptanone

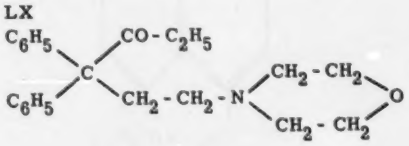
CB 11, heptalgine, etc., has been placed on the market in England, and is stated to be significantly less toxic than methadone, with equal analgesic activity.[46] Claims for high activity and comparatively favourable toxicity have been put forward by Ofner, Thorp and Walton[47] for the piperidino-analogs of both methadone and isomethadone.



3. *Modifications of the ketonic side-chain*

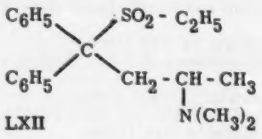
Replacement of the entire -CO-C_2H_5 chain by -O-COR in the analgetically active compound LX led to complete loss of activity, in contrast to the effect of the replacement of -COOR by -O-COR in pethidine.[48] Replacement of -CO-C_2H_5 by -COOR results in reduced activity (Eddy, Touchberry, Lieberman, loc. cit.).

LX



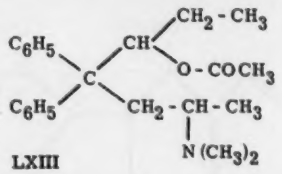
Modifications of the carbonyl group alone point to a strong specificity. However, activity is retained in the remarkably stable ketimines* obtained as intermediates in the synthesis of methadone and its analogs; also the acetates of those imines are active analgesics.[49]

Replacement of the carbonyl by the sulfone-group equally leads to highly active analgesics.[50] Of the compounds prepared, Win 1161-2 (LXII) was the best one. It is claimed to combine the activity of methadone with greatly reduced toxicity. It has been resolved into optical antipodes[51], of which the l-isomer is described as one of the most powerful analgesics.[52]



LXII

Reduction of the keto-group of methadone and isomethadone to a secondary hydroxyl has been studied in detail.[53, 54] The reduction succeeds in both cases with $LiAlH_4$, in the case of methadone also on catalytic hydrogenation. Only one of the two possible diastereomers was formed in either case. The resulting methadols and isomethadols were found to be only weakly active, but their esters are strongly analgetic (Eddy, Touchberry, Lieberman, loc. cit.); as a matter of fact, the one of the diastereomeric acetylmethadols (LXIII) resulting from reduction of l-methadone, followed by acetylation, is stated by Chen (loc. cit., p. 91) to be twice as active as d,l-methadone[54, 55] while the diastereomer obtained in an analogous manner from d-methadone has created much interest through its prolonged activity.

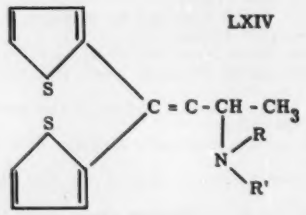


LXIII

One further group of compounds should be mentioned, which, although related to methadone, does not fit into any of the above sub-groups.

Adamson and Green[56] claim that compounds of the type LXIV are as active analgesics as morphine in the rat. The structural resemblance to methadone is unmistakable, but the absence of the quaternary carbon atom, present in nearly all other analgesics, makes this group of compounds theoretically interesting. The compound LXIV with R=R'=C_2H_5 has been designated as C-49.

LXIV



Other Series of Completely Synthetic Analgesics

It remains for us to mention a few of the many synthetic compounds which cannot be included in any one of the three preceding groups, and for which claims of analgesic activity have been made in published articles or patents. None of the numerous substances seem to have attained practical importance. For a more complete review we refer to the article by Bergel and Morrison loc. cit.

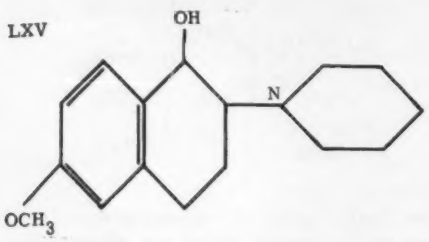
* See formula LXI, Chart IX.

Many derivatives of 1, 2-diaryl-ethylamine have been prepared and tested. Analgesic activity had been originally claimed by Dodds *et al*[57], but the claims have been disputed. More recently Holck, Kimura and Kimura[58] have investigated the activity, in mice, of 67 compounds of this group; they found that only one substance, one of the two diastereomers of C_6H_5-CHOH-CH(NH_2)C_6H_5, had "fair" activity. Many more compounds of this type have been described by several groups of investigators.

Among a series of related tertiary amines prepared by Lee, Ziering, Berger and Heineman[59] the compound p-HOC_6H_4-CH_2-CH_2-N(CH_3)-CH_2-CH_2-C_6H_5 had the highest potency (one-seventh that of morphine). Related compounds had been described earlier by Kuelz[60].

The compound LXV was described by Scheuing and Walach[61] as the most active of a number of related substances.

LXV

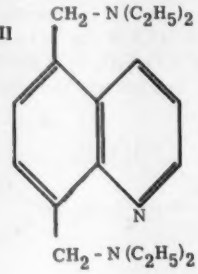


The compound LXVI is claimed by Badger, Cook, Donald, Graham and Walker[62] to be about as active as pethidine, which is remarkable in a compound not having any recognizable chemical relation to the morphine structure.

LXVI

The closely related compound LXVII, prepared by Martin and Hanslick,[63] is described as a potent analgesic.

LXVII



NOTES

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OFFICIAL

Legal Trade in Narcotics in 1949

What is the present-day situation regarding the production and the consumption of narcotics? Or, to be more specific, what observations can be deduced from the various national statistical returns on legal operations in the fields of the production and of the consumption of narcotics?

The most complete answer that can be given to the above questions at this time will be found in the following extracts from the report on statistics of narcotics for 1949, and on its work in 1950, presented by the Permanent Central Opium Board to the Economic and Social Council, at its twelfth session, held at Santiago (Chile).[1]

Present state of control

The lessons which the Permanent Central Board[2] may draw from its activities during the last three years go to confirm the conclusions which it presented in its report for 1947. In general, and in spite of minor imperfections, the machinery set up under the Conventions of 1925 and 1931 is again working fairly satisfactorily, and a good part of the difficulties which have been experienced are a direct result of the world conflict. Broadly speaking, the international control of narcotics can only be founded on the institutions and services which States have undertaken to set up and develop within the national framework. An essential function of the Permanent Central Board is to ensure that the vigilance of governments should not weaken. For this purpose it has at its disposal powers which it would not hesitate to use; but it is convinced that governments, supported by public opinion, will realize the fundamental importance of faithfully observing their international obligations, in the interests of all, and of constantly improving their national institutions. The Board will always try to give such further help as it can to governments whose task has been rendered more burdensome by political changes and economic difficulties.

Nevertheless, the Board wishes to point out that there are reasons for anxiety especially in connexion with the synthetic narcotic drugs, the production of raw materials, the consumption of diacetylmorphine and the gap in reliable statistics. These matters are all discussed later in the report, but it may be well to say here that as regards synthetic drugs, the application of the Protocol of 1948 will constitute a first essential step, though the Board naturally cannot form a judgment on this instrument without further experience.

As regards raw materials, the Board will watch with lively interest the efforts now being made by governments under the auspices of the United Nations to evolve a special machinery to limit the production of raw opium to medical and scientific needs.

Diacetylmorphine

It will be recollected that during the past two years the Board and the Supervisory Body pointed out that the *per capita* consumption of diacetylmorphine in certain countries "had increased and was very high, although the 1931 Conference recommended the abolition or restriction of the use of this particularly dangerous drug". The views of the Board and Supervisory Body were communicated to the World Health Organization, the attention of which was called to the opinions expressed on the use of diacetylmorphine and on the problems in medical practice which it raised.

The Board and Supervisory Body have been informed that in the spring of this year, the World Health Organization, referring to the statements of the Board and Supervisory Body and quoting a report of Professor

[1] Document E/OB/6.

[2] The membership of the Board is as follows: Professor H. Fischer (Switzerland), Sir Harry Greenfield, C.S.I., C.I.E. (United Kingdom), Mr. Herbert L. May (United States of America), Dr. P. Pernambuco Filho (Brazil), Professeur P. Reuter (France), Dr. M. Ristic (Yugoslavia), Professor S. Tavat (Turkey), Dr. Y. N. Yang (China). At its fifty-fifth session, June 1950, the Board re-elected Mr. Herbert L. May, President, and Sir Harry Greenfield, Vice-President, for a period of one year.

Fischer, a member of both bodies, informed governments that the Expert Committee on Drugs liable to produce Addiction of the World Health Organization is of the opinion that further information is urgently needed as to the reasons governing the present use of diacetylmorphine in some countries, particularly with regard to its possible dispensability. The letter of the World Health Organization adds that the situation is certainly different from that of earlier years owing to the availability of other morphine derivatives and the new synthetic substances with opiate effect which have since been developed; and that physicians might be more easily inclined to renounce the use of a drug which, from the addiction point of view, is certainly the most dangerous morphine derivative.

The Board is glad that these steps have been taken and hopes that they will have favourable results.

Synthetic narcotic drugs

The Protocol of 19 November 1948, by virtue of which synthetic drugs may be brought under the international control established by the Convention of 1931, entered into force on 1 December 1949. Moreover, the World Health Organization, following the sessions of its Expert Committee on this subject held in January 1949 and January 1950, designated certain synthetic drugs as capable of producing addiction.

But, at the date of the present report, synthetic narcotic drugs were not yet subject to international control, for it was only recently that a State Party to the abovementioned Protocol sent the notification provided for in article 1, paragraph 1, of this instrument, and the ensuing procedure had not yet been completed.

Some governments, however, have been supplying statistics on the movement of these substances for three or four years.

Trends in the licit movement of narcotic drugs during 1949

The present chapter sets forth the most significant facts regarding the trends in the licit movement of narcotic drugs during 1949.

The statistics for 1949 supplied by governments to the Board under the International Conventions of 1925 and 1931 are not yet complete. Furthermore, some of the statistics received are open to question. The extent to which gaps and defects in statistical returns affect the present analysis varies from substance to substance.

A. Raw Materials

(1) *Raw opium*

All the countries where there is licit production of raw opium, except the USSR, have reported their 1949 production figure to the Board.

If the 1949 figures so far provided by producer countries were accepted unreservedly, it would appear that in the majority of them a distinct downward trend occurred in that year:

Production of Raw Opium

	1947 *Tons*	*1948* *Tons*	*1949* *Tons*
India	429.7	342.2	220.0
Turkey	302.7	380.2	10.4
Iran	3.5	21.3	199.6
USSR	73.0	75.0	?
Yugoslavia	23.4	21.5	0.5
Bulgaria	3.4	4.4	0.7
Other countries	0.1	0.1	—
Total	835.8	844.7	431.2 (incomplete)

In view, however, of the gaps and defects mentioned above, the Board believes that in 1949, as always, the real total of raw opium production in a number of countries, and hence total world production, remains unknown.

The same applies to opium used for the manufacture of morphine in 1949, but in this case the gap is due to lack of the annual statistics from the USSR, Poland and Czechoslovakia. In other countries, the amounts of opium used for this purpose during the last three years were as follows:

Raw Opium used for the manufacture of Morphine

	1947 *Tons*	*1948* *Tons*	*1949* *Tons*
In opium-producing countries (the USSR excluded)	11.6	25.7	23.6
In other countries (Poland and Czechoslovakia excluded)	367.3	334.8	317.7
Total	378.9	360.5	341.3

Those amounts of raw opium produced 42 tons of morphine in 1947, 40.9 tons in 1948 and 39.4 tons in 1949, a yield of 11.1 per cent, 11.3 per cent and 11.5 per cent respectively. In addition, morphine was manufactured from poppy straw (see paragraph (2) below).

The only information supplied to the Board regarding prepared (smoking) opium with respect to the year 1949 is as follows: Thailand declared a production of 17 tons (obtained from 20 tons of raw opium) and a consumption of 16 tons; Indonesia, a consumption of 77 kilograms.

(2) *Poppy straw*

This raw material of morphine is not covered by the international conventions on narcotic drugs. Most of the countries employing it, however, declare to the Board the amounts used in manufacture and the amounts of morphine thus produced.

The latter were 4.2 tons in 1947, 7.8 tons in 1948 and 9.7 tons in 1949. The figures for the years 1947 and 1948 do not include production in Poland (0.8 and 0.6 ton respectively) since in the statistics of that country it is impossible to distinguish the morphine thus

obtained from the morphine extracted from raw opium. The 1949 figure does not include production in either Poland or Czechoslovakia, those countries not yet having reported it.

(3) *Coca leaves and crude cocaine*

So far as the Board is aware, there are at present four countries which produce coca leaves: Bolivia, Colombia, Indonesia and Peru. Only two of them, Colombia and Indonesia, have declared their 1949 production figure (210 and 4.5 tons respectively); they are not the largest producers, and, according to the declaration made by Colombia, the figure of 210 tons is to be regarded as an approximate one. The situation in this respect is neither better nor worse than it was in the past, and the Board has never been able to determine even approximately the total world production of this substance.

In addition, Peru, also a manufacturer of cocaine (chiefly crude cocaine), has not yet declared either the amount of coca leaves used in 1949 for this manufacture (in 1946-1948: an average of 160 tons per annum) or the amount of crude cocaine obtained (in 1946-1948: an average of one ton per annum). It is impossible, therefore, to calculate the corresponding world totals.

The Board is no better informed as to the amounts of coca leaves consumed (chewed) in two important coca-leaf producing countries, namely Bolivia and Peru; the national authorities concerned may not know the amounts themselves. In Colombia the responsible authorities have declared that the amounts so consumed came to about 180 tons in 1947, 180 tons in 1948 and 170 tons in 1949. Argentina is the only country not producing coca leaves in which the leaves were consumed in that manner: 452 tons in 1947, 181 tons in 1948 and 313 tons in 1949, imported from Bolivia and Peru.[3]

In 1949, four cocaine producing countries, the USA, the United Kingdom, Switzerland and France, together produced 1,390 kilograms of the drug, or 87 per cent of world production that year; as usual, they imported the necessary raw materials: the USA, coca leaves, and the other three countries, crude cocaine. The amounts of raw materials used for manufacturing cocaine in those countries during the last three years are as follows:

	Coca leaves	*Crude cocaine*		
	In U.S.A.	*In United Kingdom*	*In France*	*In Switzerland*
	Tons	*Kg.*	*Kg.*	*Kg.*
1947.....	158	496	302	15
1948.....	175	309	283	194
1949.....	158	526	90	345

[3] Further information on the chewing of coca leaves may be found in the Report of the Commission of Enquiry on the Coca Leaf, May 1950, United Nations document E/1666.

Lastly, the amounts of coca leaves used in the USA for the preparation of non-narcotic coca-flavoured beverages fell from 129 tons in 1947 to 6 tons in 1948 and 0 in 1949.

(4) *Indian Hemp*

This plant is the basis of medicinal preparations, which are little used (some 600 kilograms a year), and of non-medicinal products consumed by addicts in several parts of the world under the names of hashish, marihuana, charas, ganja, etc. The statistics to be supplied to the Board under the Convention of 1925 relate only to imports, exports, confiscations effected on account of illicit imports and exports, and also, in the case of the medicinal preparations, to consumption and stocks. The Board, considering that such information depicts only a negligible part of the movement of these substances, has always refrained from commenting on it.

B. Manufactured Drugs

(1) *Morphine*

It is not at present possible to determine whether the steady increase in world production of morphine that has taken place in recent years continued in 1949, since the annual statistics of the USSR, Czechoslovakia and Poland are not available. Very probably, however, it has done so. Those three countries apart, 49.2 tons of the drug were produced in the world in 1949, as against 48.2 tons in 1948, an increase of 2.1 per cent. The 1948 production of the USSR was 6.8 tons, and that of Czechoslovakia and Poland together 1.4 ton. Assuming that the volume of production in those three countries was the same in 1949 as in 1948, the 1949 world total would be 57.4 tons. That would be a new record, the highest figure previously recorded being 56.5 tons in 1948.

These figures show that world production of morphine—the USSR, Czechoslovakia and Poland excluded—increased by 0.9 tons in 1949 above the previous year's level. This upward trend did not appear in all producing countries; in some there was a pronounced decrease. The most considerable increases and decreases were as follows:

Production of Morphine

	1948	*1949*	*Difference*	
	Tons	*Tons*	*Tons*	*Per cent*
(i) Increase:				
United Kingdom	7.3	10.6	+3.3	+ 45
Hungary	2.1	4.8	+2.7	+128
(ii) Decrease:				
United States	17.3	15.2	−2.1	− 12
France	7.4	6.4	−1.0	− 13
Germany	4.3	3.6	−0.7	− 16
Switzerland	3.8	2.9	−0.9	− 24

It is to be noted that morphine production in Hungary more than doubled between 1948 and 1949, and this year reached the highest figure so far recorded by the Board for that country; 95 per cent of that morphine was used to manufacture codeine and dionine (chiefly the former), most of which was exported.

Morphine production figures, and figures for its conversion into other substances throughout the world, always follow a common trend, since the greater part (91 per cent) of morphine produced is so converted. The total world figures—the USSR, Czechoslovakia and Poland excluded—for morphine used for conversion rose from 43.2 tons in 1948 to 44.9 tons in 1949, an increase of 4 per cent. Assuming that the amounts used for conversion purposes in the three countries excluded were the same in 1949, as in 1948, the world total for 1949 under this head would be 52.2 tons, a new record. In 1949, manufacture of codeine continued to account for the greater part (81 per cent) of the morphine produced, and thus to be the determining factor in morphine production both as regards volume and trend.

The world total of morphine not subsequently converted into other drugs (i.e., of morphine available as such), excluding the figures for the USSR, Czechoslovakia and Poland, decreased from 5 tons in 1948 to 4.3 tons in 1949. If the amounts under this head in the three countries excluded were the same in 1949 as in 1948, the world total would be 5.2 tons, but would remain lower than it usually was before the war.

(2) *Synthetic narcotic drugs*

There are at present about a dozen synthetic narcotic drugs the effects of which, both beneficial and harmful, are in general similar to those of morphine. The use of two of them:

(i) Pethidine (hydrochloride of 1-methyl-4-phenyl-piperidine-4-carboxylic acid ethyl ester), also known under the names of Demerol, Dolantin, Dolosal, Isonipecaine, Dolental, etc., and

(ii) Methadone (hydrochloride of 4:4-diphenyl-6-dimethyl-aminoheptan-3-one), also known under the names of Amidone, Miadone, Adanone, Dolophine, Physeptone, etc.,

as substitutes for morphine appears to be more or less universal. Although these drugs do not as yet come under the provisions of the 1931 Convention, a number of governments have included them, in some cases for three years and in others for four, in the statistics with which they provide the Board.

The comparison made in the following table between the consumption of morphine and pethidine in the United States, the United Kingdom and France, in 1936, 1948 and 1949, indicates that the latter drug is gaining in importance, and a similar trend is reflected in the other countries which have submitted statistics; but the experience so far gained does not justify the drawing of definite conclusions.

Consumption of Morphine and Pethidine

	Morphine			*Pethidine*			*Morphine + Pethidine*		
	1936	*1948*	*1949*	*1936*	*1948*	*1949*	*1936*	*1948*	*1949*
		Kilograms			*Kilograms*			*Kilograms*	
United States	2,226	1,582	1,605	0	2,613	4,412	2,226	4,195	6,017
United Kingdom	709	747	876	0	418	609	709	1,165	1,485
France	329	206	135	0	226	238	329	432	373
TOTAL, for the above countries	3,264	2,535	2,616	0	3,257	5,259	3,264	5,792	7,875

The consumption of methadone in those countries, in 1949, was as follows: USA, 1,397 kilograms; United Kingdom, 46 kilograms; France, 0.

So far as the three countries shown in the above table are concerned, the production of pethidine, as compared with that of morphine produced for use as such, in the years 1947, 1948 and 1949, was as follows:

Production of Morphine and Pethidine

	Morphine as such			*Pethidine*		
	1947	*1948*	*1949*	*1947*	*1948*	*1949*
		Kilograms			*Kilograms*	
United States	2,379	1,824	1,486	5,144	4,492	4,791
United Kingdom	931	110	1,087	1,155	843	704
France	371	496	569	234	177	297
TOTAL, for the above countries	3,681	2,430	3,142	6,533	5,512	5,792

(3) *Diacetylmorphine*

With one exception, Czechoslovakia, the twelve countries engaged in licit manufacture of diacetylmorphine during the past three years have declared their production figures for this drug in 1949. The total thus declared for the whole world is 523 kilograms (the absence of Czechoslovak production figures is unlikely to affect the position, since the average annual figure over eight years was only 1 kilogram. This total of 523 kilograms constitutes a decrease of 316 kilograms, or 38 per cent, compared with the total for the year 1948. The decrease occurred in all producer countries but one, the most marked cases being the following:

Production of Diacetylmorphine

	1948	1949	Decrease	
	Kg.	Kg.	Kg.	Per cent
United Kingdom	300	149	151	50
Italy	278	223	55	20
France	79	25	54	68
Finland	73	25	48	66
Switzerland	45	3	42	93

The exception was Hungary, where production of the drug rose from 4 kilograms in 1948 to 69 kilograms in 1949.

World production of diacetylmorphine has not been very stable in recent years, and it would be premature to interpret the decrease in 1949 as a sign of similar decrease in demand for the drug.

(4) *Dihydrohydroxycodeinone, dihydrocodeinone, dihydromorphinone, acetyldihydrocodeinone and methyldihydromorphinone*

All the thirteen countries producing one or other of these drugs in the last three years have declared their 1949 production figures to the Board, with the exception of Czechoslovakia (average production in that country during the last three years was, however, less than 1 kilogram). The amount manufactured in the world in 1949 (927 kilograms) is 39 kilograms lower than in 1948. Production was, however, 380 kilograms, or 65 per cent higher in 1948 than in 1947, and had already reached record figures both in 1947 and 1948. It is interesting to note, therefore, that the big increase in demand for those drugs recorded in 1948 is confirmed by the figure for world production in 1949.

Another interesting point is that the total of the amounts produced in 1949 in eleven of the thirteen countries manufacturing these drugs decreased by 258 kilograms in relation to 1948, and that the decrease was offset by an increase of 204 kilograms of the production in Germany and 15 kilograms in the Netherlands. In Germany, this production rose to 416 kilograms in 1949, and that country has thus regained the position of chief producer of the drugs in question occupied by it before the war.

(5) *Codeine*

In the case of this drug, as in that of morphine, it is not yet possible, in the absence of figures for the USSR, Czechoslovakia and Poland, to determine whether world production increased in 1949, as it had regularly done during the previous years. It is almost certain, however, that, as in the case of morphine, it did so increase. Production, those three countries excepted, rose from 37.7 tons in 1948 to 39.5 tons in 1949, that is to say 4.8 per cent. The amount manufactured by the three countries in 1948 was 6.5 tons and, assuming it to have been the same in 1949, the world total for that year would come to some 46 tons. That would be a new record, the previous record being 44.2 tons in 1948.

(6) *Dionine*

What has just been said of codeine applies equally to dionine. In this case, however, the absence of statistics for Czechoslovakia and Poland is of little importance, since production in those countries was negligible or non-existent. World production, excluding production in the USSR, for which 1949 figures are still lacking, rose from 3,558 kilograms in 1948 to 4,206 kilograms in 1949. Assuming that the USSR produced the same amount of the drug in 1949 as in 1948, i.e., 585 kilograms, the world total for 1949 would be 4,791 kilograms. That would be the highest figure so far recorded, the previous maximum being 4,143 kilograms in 1948.

(7) *Cocaine*

World production of cocaine increased from 1,506 kilograms in 1948 to 1,594 kilograms in 1949, i.e., 6 per cent; it remains, however, among the smallest recorded by the Board and is about one-half of the figure reached in the years preceding the war.

According to the statistics supplied by the competent authorities in the USSR, domestic cocaine production before the 1939-1945 war averaged about 270 kilograms a year and was used to meet the country's medical and scientific requirements. Since the end of the war, according to the same statistics, no cocaine or raw materials for cocaine (coca leaves, ecgonine, crude cocaine) have been produced or were in stock in the USSR; nevertheless, 198 kilograms of crude cocaine were exported to Switzerland in 1948 and 1949. This country subsequently re-exported pure cocaine to the USSR.

Conclusions

In spite of the absence of some important statistics of manufactured drugs, the following trends are to be observed. The production of morphine, codeine and dionine continued to increase in 1949 and, without a doubt, reached a record figure during that year; but, as a matter of fact, the quantity of morphine produced for

use as such has slightly decreased during recent years. Allowance must, however, be made for the fact that pethidine (Dolantin, Demerol, Dolosal, etc.), a synthetic drug of almost world-wide use as a substitute for morphine since the end of the 1939-1945 war, is at present being turned out in quantities superior (at least, in weight, if not in therapeutic potency), to the amount of morphine produced for use as such. At the date of the present report, pethidine has not yet been brought under the control established by the international conventions on narcotic drugs.

The production of a group of drugs comprising dihydrohydroxycodeinone, dihydrocodeinone, dihydromorphinone, acetyldihydrocodeinone and methyldihydromorphinone, continued at the record level it attained in 1948. The production of diacetylmorphine and of cocaine is lower than it generally was before the 1939-1945 war.

The Board has had frequent occasion to complain in the foregoing paragraphs of the absence of statistics from a few countries which are large producers of one or other of the narcotic drugs covered by the International Conventions of 1925 and 1931. It gives it pleasure, on the other hand, to be able to mention, in conclusion, that the majority of the other countries have supplied it with all the statistics provided for under those Conventions and have duly rendered account of their supplies of narcotic drugs. For some of them, and, in particular, the countries manufacturing and exporting such substances, the present system of international control throws a considerable burden of work on various governmental authorities, and the Board wishes to express its high appreciation of the collaboration and support it has received from them in the performance of its duties.

The Work of the Commission on Narcotic Drugs at its Fifth Session

At its fifth session, the Commission on Narcotic Drugs dealt primarily with three main long-range problems: the interim agreement for the limitation of the production of opium, a simplified and improved convention to replace the existing instruments on narcotics, and the question of the chewing of the coca leaf in some countries of Latin America. In view of the importance of that programme, the introduction to the report of the Commission to the Economic and Social Council[1] is reproduced below.

* * *

1. While the primary task of the Commission on Narcotic Drugs is and must continue to be, to bring under review the working of the international control of narcotic drugs in all its aspects, the Commission is at the present time increasingly concerned with the study of new developments in the direction of increasing the range and simplifying and improving the efficiency of that control.

2. At its fifth session, which was held at Lake Success, New York, the Commission had under consideration three major proposals, each of which is concerned with an important advance in the field of the international control of narcotic drugs.

3. The first of these was the proposal for an interim agreement to limit the production of opium to that required to meet the world's medical and scientific needs and to establish for this purpose an international monopoly through which the trade in opium would be conducted.

4. The Commission had before it the report of its *Ad Hoc* Committee of the Principal Opium-producing Countries, which met at Ankara in 1949, the reports of the Meeting of Representatives of the Principal Drug-manufacturing Countries, and of the Joint Committee of the Principal Opium-producing Countries and of the Principal Drug-manufacturing Countries, which met at Geneva in August 1950, and the Joint Committee's report on the second part of its session held at New York from 14 to 30 November 1950.

5. The Commission noted with satisfaction that substantial progress had already been made since the consideration of this proposal was initiated by the appointment of the *Ad Hoc* Committee which met at Ankara. The principle of limitation of production of opium had been accepted; the shares of production to be assigned to each producing country had been determined; there was agreement as to the means to be envisaged to secure the limitation of production, namely, the creation of an International Opium Monopoly; the paramount importance of inspection for the proper functioning and successful operation of the scheme had been affirmed; and the main provisions of a draft interim agreement prepared by the Secretary-General had been studied, and in certain respects amended. The Joint Committee had nevertheless been unable to find solutions to four questions, including the major question of the basic price at which the International Monopoly should conduct its operations, which would have to be resolved before any interim agreement could be brought into force. With a view to making further progress as rapidly as possible the Commission on Narcotic Drugs decided to recommend to the Economic and Social Council that its sixth session should be held during April and May 1951, and should be devoted in the main to a further consideration of these questions. Account would be taken, in this further consideration, of a proposal made by the Joint Committee, as to possible further procedure, namely that should a satisfactory solution to all these questions ex-

[1] See document E/CN.7/216.

cept that of price be found, the interim agreement might be elaborated, opened for signature, and even ratified, in a form which would permit of the International Monopoly undertaking trade in opium only after unanimous agreement on price had been reached.

6. The second of the major proposals considered by the Commission was that for a simplified and improved convention to replace the eight existing instruments on narcotic drugs, and to contain provisions for the limitation of the production of raw materials. The Commission had before it a draft of such an instrument, prepared by the Secretary-General in accordance with the request of the Commission at its fourth session and accompanied by a detailed commentary on the provisions of the draft. The Commission recorded its appreciation of the care and skill with which both the draft and the commentary had been prepared and it devoted some time to a discussion of the main principles of the new instrument. The discussion was in the nature of an exchange of views, since there was not time to reach conclusions on the many and complex issues which the new proposals involve and which require detailed study. The Commission felt therefore that it would be premature at the present stage to communicate the draft to Governments for their observations, as it was authorized to do, if it thought that course desirable, by Resolution 315 (XI) of the Economic and Social Council. It considered, however, that it would be of advantage that the views of the Governments represented on the Commission should be formulated, in the light of the discussion which had already taken place in the Commission, and made available to the Commission for further consideration, if time permits, at its sixth session, in order that the conclusions then reached by the Commission might be embodied in a revised draft, which would then be considered by the Commission at its seventh session early in 1952.

7. The third of the major questions which was studied by the Commission was the problem of coca leaf chewing in Bolivia and Peru. The Commission had before it the Report to the Economic and Social Council of the Commission of Enquiry which visited Bolivia and Peru towards the end of 1949. The main conclusion of the report is that coca-leaf chewing has harmful effects, and that since the habit is the consequence of a number of unfavourable social and economic factors, the solution of the problem involves two fundamental and parallel aspects: the need for improving the living conditions of the population amongst which chewing is a general habit, and the need for initiating simultaneously a governmental policy to limit the production of coca leaf, to control its distribution, and eradicate the practice of chewing it. The Commission of Enquiry made detailed recommendations in regard to these two aspects in its report. The Commission on Narcotic Drugs recorded its appreciation of this report and of the co-operation given to the Commission of Enquiry by the Governments of Bolivia and Peru.

8. At the invitation of the Commission on Narcotic Drugs a representative of the Government of Bolivia attended at the discussion of the report, and statements were made by the representatives of Bolivia and Peru, which expressed dissatisfaction with the conclusions and recommendations of the Commission of Enquiry on the ground that this Commission had not itself undertaken an expert scientific investigation of the medical and physiological factors involved, and that the findings upon which these conclusions and recommendations are based are not accepted by certain medical and scientific authorities in these countries who have given the question special study. The Commission on Narcotic Drugs considered that it would be desirable that the Economic and Social Council, when studying the report, should have before it the observations of the Commission of Enquiry upon the opinions expressed by the representatives of Bolivia and Peru, and it therefore decided to request the Commission of Enquiry to forward these observations to the Secretary-General by 1 March 1951 so that the Secretary-General might transmit them to the Council. It further decided to recommend to the Council that the report and the observations of the Commission of Enquiry should be forwarded to the Governments of Bolivia and Peru with a request that they should communicate their respective observations thereon to the Secretary-General before 15 September 1951; and that the Commission on Narcotic Drugs should examine the question further, taking all available information into consideration, at its seventh session, with a view to submitting recommendations to the Council as soon as possible thereafter.

United Nations Documents of Scientific Interest in the Field of Narcotics

A

In 1949, at its fourth session, the Commission on Narcotic Drugs discussed the possibility of determining the origin of opium seized from the illicit traffic by means of physical and chemical tests. The representative of the United States offered to put laboratory facilities at the disposal of the Secretariat for the study of this problem.

On 6 July 1949 the Economic and Social Council adopted resolution 246 F (IX), requesting the Secretary-General "to further, within the means available, research on the methods of determining the origin of opium", and authorizing him to accept the offer of the United States.

A general programme of international scientific research on opium was started, in which the collaboration of both producing countries and countries able to do advanced scientific research on opium was requested.

B

During 1950, and since, members of the Secretariat have carried out scientific research on opium. A stock of opium samples has been obtained from a number of the producing countries, and a general distribution of samples to scientists recommended by governments to participate in the research began early in 1951.

The following documents were issued as Commission documents:

E/CN.7/117, which included the following articles: (*a*) on determining the country of origin of opium; (*b*) the identification of methadon by microcrystals (this is not connected with the opium problem, but also has scientific interest); (*c*) photomicrographs of opium crystals; (*d*) some minor alkaloids of opium, alkaloid 1, "porphyroxine-meconidine"; (*e*) opium alkaloids—narceine; (*f*) opium alkaloids—thebaine.

E/CN.7/117/Add.1: Opium alkaloids; codeine.

E/CN.7/117/Add.2: Examination of opium for distinguishing characteristics; some tentative methods.

(These papers were communicated by the representative of the Government of the United States of America.)

E/CN.7/195: The comparative determination of "porphyroxine-meconidine" (Secretariat).

E/CN.7/202: Determination of codeine in the lime-water extract of opium (Secretariat).

E/CN.7/207: Further data on "porphyroxine-meconidine" (contribution from Canada by C. G. Farmilo and P. M. L. Kennett).

A general account of the attack upon this problem was given in the first issue of this *Bulletin,* October 1949, "Determining the Origins of Opium".

At its fifth session, in December 1950, the Commission on Narcotic Drugs discussed the value of obtaining an improved assay of legitimate opium for its morphine and codeine content, and decided to request the Secretary-General to continue the chemical research on opium with special attention to the determination of these alkaloids, and also "to explore the possibilities of research into the methods of determining the origin of opium by scientific means other than those referred to in resolution 246 F (IX)", such as pharmacological tests.

A short discussion of the fundamental problems remaining in the chemistry of opium is included in this *Bulletin.* (Present State of the Chemistry of Opium and its Future Possibilities.)

C

It has been decided that future scientific articles on opium issued by the Division on Narcotic Drugs will be in a separate series with the designation ST/SOA/SER.K, under the general title of: "The Assay, Characteristics, Composition, and Origin of Opium".

The first article in this series is ST/SOA/SER.K/1, "The determination of morphine in opium by extraction: a new method".

D

The analysis of opium for morphine is useful not merely in helping to determine the origin of contraband opium seized from the illicit traffic; it is of paramount importance in the commercial and medical evaluation of licit opium, and in national and international accounting of opium used and drugs produced. It is considered, therefore, that the paper will have considerable interest to chemists in these various fields.

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[2] This is the third part of a general bibliography of Cannabis Sativa, begun in volume II, no. 1, of the *Bulletin of Narcotics,* January 1951. See introduction to part I in that issue.

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ABBREVIATIONS

PCOB stands for "Permanent Central Opium Board"

SB stands for "Supervisory Body"

NOTE

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